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Drinking Water Criteria Document for Pentachlorophenol

Syracuse Research Corp., NY

Prepared for:

Environmental Protection Agency, Cincinnati, OH

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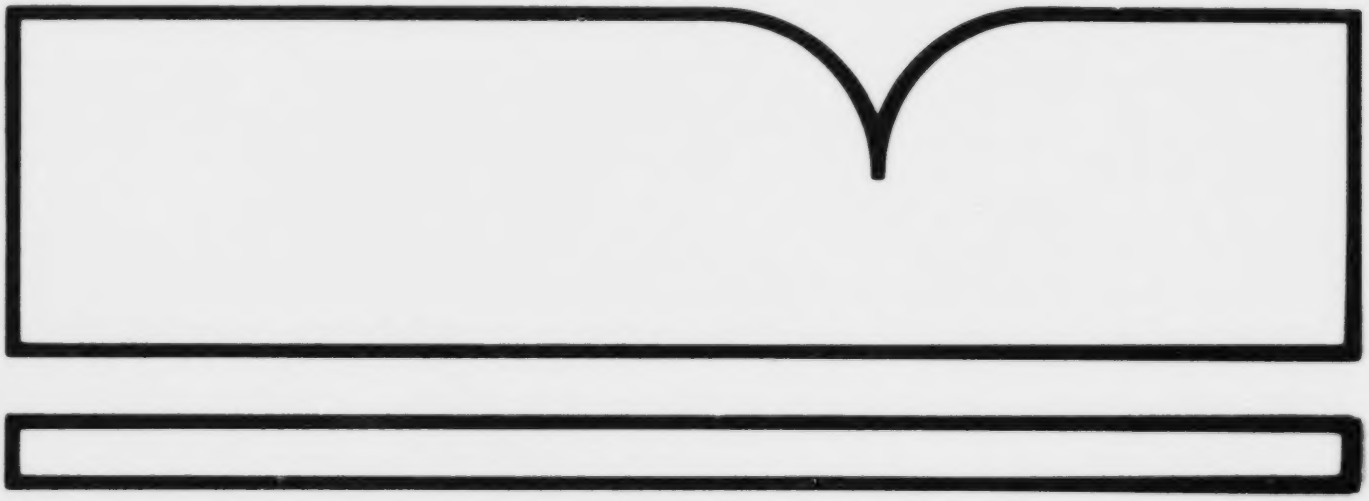

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Prepared for

OFFICE OF DRINKING WATER

Prepared by

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
U.S. Environmental Protection Agency
Cincinnati, OH 45268

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16. ABSTRACT

This document deals with the drinking water health effects of Pentachlorophenol through the review of several studies. These studies include animal and humans. Physical and chemical properties are discussed. Carcinogenicity of the compound is reviewed and evaluated through various studies. Any existing guidelines and standards are presented.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group
health effects, drinking water, animal studies, cancer risk, cancerous, criteria standards, criteria document, human studies, Pentachlorophenol		

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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1984; however, more recent data may have been added during the review process.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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LIST OF ABBREVIATIONS

bw	Body weight
DD	Dibenzo-p-dioxin
DF	Dibenzofuran
DMBA	Dimethylbenzanthracene
DWEL	Drinking water equivalent level
ENU	Ethylnitrosourea
FEL	Frank-effect level
GC/MS	Gas chromatography/mass spectrometry
HA	Health Advisory
HCDD	Hexachlorodibenzo-p-dioxin
i.p.	Intraperitoneal
i.v.	Intravenous
LD_{50}	Dose lethal to 50% of recipients
LD_{Lo}	Lowest dose observed to cause lethality
LDH	Lactic dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MSB	Moloney sarcoma virus
MSV	MSV-transformed sarcoma virus
NaPCP	Sodium pentachlorophenate
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NaPCP	Sodium pentachlorophenate
PCP	Pentachlorophenol
ppb	Parts per billion
ppm	Parts per million
RfD	Reference dose
s.c.	Subcutaneous
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure level
TCDD	Tetrachlorodibenzo-p-dioxin
TCH	Tetrachlorohydroquinone

I. SUMMARY

Pentachlorophenol (molecular weight, 266.34) forms colorless crystals with a definite phenolic odor. This compound is stable in aqueous solution with a solubility of 20 mg/ℓ at 30°C, though microbial and photochemical degradation may occur. Although pentachlorophenol may be obtained as a pure compound, technical and commercial grades are contaminated with a number of highly toxic impurities, including chlorinated dibenzo-p-dioxins, dibenzofurans and hexachlorobenzene.

Pentachlorophenol is rapidly absorbed following oral, dermal or inhalation exposure. The major tissue depots of pentachlorophenol are the liver, kidneys, brain, spleen and fat. The tissue/plasma concentration ratio is less than would be expected when there is extensive protein binding in the plasma. Following a single dose, pentachlorophenol is rapidly excreted with a half-life of ~10 hours, indicating that there should be little tendency for pentachlorophenol to accumulate in the body. During chronic exposure, however, the excretion kinetics appear to be altered, resulting in a biological half-life of ~20 days. Therefore, blood levels during chronic exposure are generally higher than would be predicted from single-dose models. At the same time, a tolerance to the toxic effects of pentachlorophenol appears to develop, at least in rats. Blood levels 2-5 times those observed following a single lethal dose may be reached before death occurs. The major route of excretion is the urine, with lesser amounts being excreted in the feces and only trace amounts appearing as CO_2 in the expired air.

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Signs of toxicity in animals following either acute or chronic oral exposure are similar. There is an initial rise in body temperature and respiration rate, with respiration becoming slower and dyspneic as coma develops. Death is characterized by cardiac and muscular collapse with terminal asphyxial convulsions. Following dermal exposure, the signs of toxicity are similar to those following oral exposure with the addition of local dermal irritation at the site of application. Rigor mortis occurs quickly and is unusually pronounced. Liver and kidney involvement is often noted in cases of chronic poisoning. Reported oral LD_{50}s range from 27 to >300 mg/kg bw; however, the lower values probably reflect contamination with the highly toxic chlorinated dibenzo-p-dioxins and dibenzofurans.

Recently, NTP (1989) provided "sufficient" evidence of carcinogenicity of pentachlorophenol in mice. This evidence, along with the absence of "sufficient" evidence of carcinogenicity of pentachlorophenol from epidemiologic studies, results in pentachlorophenol being classified as a U.S. EPA Group B2 compound - probable human carcinogen. The compound is marginally mutagenic.

Pentachlorophenol is fetotoxic and has adverse effects on reproduction in laboratory rats. Treatment with pentachlorophenol results in increased resorptions and alterations in the sex ratio of rat pups with males predominating in the surviving pups. A number of skeletal anomalies have been reported; however, the investigators considered these to be toxic rather than teratogenic effects. In rats, the most sensitive period to toxic effects occurs on days 8-10 of gestation. Little pentachlorophenol reaches the fetus once the chorioallantoic placenta has formed.

In humans, local irritation, allergic responses and systemic effects have been reported. Pentachlorophenol poisoning is characterized by a profuse sweating, often accompanied by fever, weight loss and gastrointestinal complaints.

The major mechanism of pentachlorophenol toxicity is believed to be the uncoupling of cellular oxidation and phosphorylation. This results in an increase in the basic metabolic rate, which may account for many of the symptoms observed in cases of pentachlorophenol poisoning. Pentachlorophenol may affect the toxicity of other compounds by a variety of mechanisms. The best characterized of these involves alterations of metabolism, either through induction of microsomal enzymes or inhibition of sulfation.

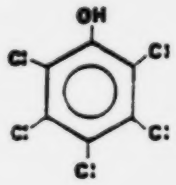
Based on the reported toxicities of pentachlorophenol in experimental animals, 1-day, longer-term and lifetime health advisories (HAs) were derived. It was recommended that the longer-term HA for a 10 kg child be adopted as the 10-day HA. The resulting value for a 1-day HA is 1.0 mg/ℓ for a 10 kg child. The 10-day HA is 0.30 mg/ℓ for a 10 kg child. The longer-term HA of 1.1 mg/ℓ for a 70 kg adult and 0.30 mg/ℓ for a 10 kg child are only slightly lower than the 1-day HAs, and the lifetime drinking water equivalent level (DWEL) of 1.1 mg/ℓ is the same as the adult longer-term HA. Water concentrations approaching the HAs for adults are likely to be unacceptable, due to organoleptic considerations.

While the available carcinogenicity studies are negative, for various reasons these studies are considered inadequate for an assessment of pentachlorophenol's human carcinogenic potential. Therefore, pentachlorophenol is classified according to the U.S. EPA's Guidelines for Carcinogen Risk Assessment in Group D: Not classified.

II. GENERAL INFORMATION AND PROPERTIES

Structure and Identification

Pentachlorophenol is also known as PCP and pentachlorohydroxybenzene and is present in a variety of products including Penta, Santophen 20, Dowicide 7, Chlorophen, Penchloro, Sinituho, Weedone, Santobrite, EP 30, Liropren, Lauxtol, Fungifen, Durotox, Thompson's Wood Fix, Term-i-Trol, Permite, Penta-Kil, Pentasol, Penwar, Perotox, Permacide, Permagard, Permatox and Chem-tol. The structure of pentachlorophenol is as follows:



Molecular formula: C_6Cl_5OH

Molecular weight: 266.34

The Chemical Abstracts Service (CAS) registry number for this compound is 87-86-5 and the Registry of Toxic Effects of Chemical Substances (RTECS) number is SM6300000.

Chemical and Physical Properties

The physical properties of pentachlorophenol are summarized in Table II-1. The commercial product exists as white to light yellow beads, powder or crystals and has a characteristic strong odor when hot. In the pure form, pentachlorophenol forms colorless crystals with a phenolic odor (BCPC, 1977).

TABLE II-1

Physical Properties of Pentachlorophenol

Property	Value	Reference
Molecular weight	266.34	CRC, 1982
Boiling point	309-310°C	CRC, 1982
Melting point	191°C (anhydrous)	CRC, 1982
Vapor pressure	0.00011 mm Hg at 20°C	Verschueren, 1983
Solubility*	14 mg/ℓ water at 20°C	Verschueren, 1983
	5 mg/ℓ water at 0°C	Verschueren, 1983
	soluble in ethanol, ether and benzene	CRC, 1982
	limited solubility in carbon tetrachloride	BCPC, 1977
	slightly soluble in petroleum ether	BCPC, 1977
Log octanol/water partition coefficient	5.86	Hansch and Leo, 1979
Specific gravity	1.978_1^{22}	CRC, 1982
pKa	4.74	Drahonovsky and Vacek, 1971

*Sodium pentachlorophenate is highly soluble in water.

Conversion factors for air concentrations: 1 ppm = 10.3 mg/m³
1 mg/m³ = 0.092 ppm

Pentachlorophenol photodegrades rapidly in both laboratory and rice field water with a half-life of 48 hours in a borosilicate glass flask irradiated with sunlight at pH 7.3 (Wong and Crosby, 1981). At pH 7.3 pentachlorophenol is present as the anion; at pH 3.3 the authors reported a much longer half-life (>90 hours). In natural systems, the half-life was longer due to light intensity attenuation with depth (Burns et al., 1981). Products of the photolysis were found to include 2,3,4,6- and 2,3,5,6-tetrachlorophenol, tetrachlororesorcinol, tetrachlorocatechol, 2,3-dichloromaleic acid, chloropropionic acid, 4,5-dichloro-1,3-cyclopentanedione, tetrachloro-1,4-benzoquinone and 3,6-dichloro-2,5-dihydroxyl-4-benzoquinone. When high concentrations of pentachloropnenol were irradiated, small quantities of octachlorodibenzo-p-dioxin were formed. Wong and Crosby (1981) also analyzed a stream near a wood treatment plant and found, in addition to pentachlorophenol, some 2,3,4,6-tetrachlorophenol and a dichlorophenol but no 2,3-dichloromaleic acid, a principal degradation product. Pierce and Victor (1978) also reported finding tetrachlorophenols after a pentachlorophenol spill.

Biodegradation rates for pentachlorophenol vary considerably (Alexander and Aleem, 1961; Tabak et al., 1981; Baker et al., 1981; Roth et al., 1982; Korte and Geyer, 1980; Schefer and Waelchli, 1980). This marked variation appears to be related to the initial concentration of the phenol, with higher levels apparently being toxic to the microorganisms. Alexander and Aleem (1961) reported 100% removal of a 50 µg/mℓ (ppm) solution of pentachlorophenol in 72 days using a soil suspension. Tabak et al. (1981) used a sewage seed and reported 100% degradation in 14 days at 5 µg/mℓ pentachlorophenol while at 10 µg/mℓ, 28 days were required to achieve a

99% removal. Baker et al. (1960) reported only a 1% removal of pentachlorophenol in 40 days at 100 µg/mℓ concentration from a stream at 20°C. When sediment was added, a 29% removal was achieved in 30 days.

Pentachlorophenol has a pK_a of 4.74 and, consequently, exists as the anion in most environmental surface waters (Callahan et al., 1979). As such, the log octanol/water partition coefficient (log P_{ow}) reported for the parent compound (5.86) can not be an indicator of the sorption potential of pentachlorophenol in the environment, since the anion is more soluble in water than the parent compound. No log P_{ow} value could be located in the available literature for the anion. Hiatt et al. (1960) reported that pentachlorophenol did not sorb to neutral soils but did sorb to acidic soils. The most sensitive parameter in controlling the sorption of pentachlorophenol is pH, while soil organic matter determines how much compound will sorb (Choi and Aomine, 1974). Thus, in organic rich acidic sediments, pentachlorophenol will be expected to sorb, while in slightly acidic, neutral or basic sediments, sorption will not be expected. Supporting this conclusion are the reports of Pierce (1978) and Pierce and Victor (1978), who followed the fate of two accidental spills of pentachlorophenol in a lake. Pentachlorophenol was found to sorb to leaf litter, which appeared to control its transport throughout the lake.

Pentachlorophenol has been detected in many effluent streams and in some finished drinking water (Shackelford and Keith, 1976; Buhler et al., 1973). Buhler et al. (1973) studied pentachlorophenol removal from sewage treatment plants by monitoring both the influent and effluent. They reported an aver-

age 4-28% removal. The authors also reported that pentachlorophenol concentrations in the Willamette River entering the Corvallis Taylor water treatment plant were 0.10-0.70 ppb; the plant removed ~60% of the pentachlorophenol, leaving ~40% in the finished drinking water. Wegman and Hofstee (1979) reported detecting pentachlorophenol in all 206 samples taken between 1976 and 1977 at six sites along the Rhine River and tributaries in the Netherlands. Concentrations averaged 1.13 µg/ℓ (ppb), with the highest concentration reaching 11 µg/ℓ. Between 1979 and 1980, sediment samples were taken from 35 sites, many of which were along the Rhine River and tributaries (Wegman and van den Broek, 1983). Pentachlorophenol was found in all samples with the highest levels in the Nieuwe Maas River near Rotterdam, a heavily industrialized area. Where both surface water and sediment were analyzed at the same time, the median sediment concentrations of pentachlorophenol were found to be 20 times higher than the medium water. The ratio of sediment to water concentration was highest for 2,4-dichlorophenol with the sediment concentration being 440 times higher than water. No information was provided on the composition of the sediments (i.e., percent organic matter, pH) and it is not known if the sediments provided a sink for pentachlorophenol slowly partitioning it into the water. By contrast, Wong and Crosby (1981) analyzed surface ponds and agricultural drainage water near a wood-treatment facility, and found pentachlorophenol concentrations between 1 and 300 µg/ℓ (average 22ℓ). Pentachlorophenol in well water in the area ranged between <1 and 50 µg/ℓ. Pentachlorophenol concentrations downstream in the Sacramento River water were <1 µg/ℓ.

Pentachlorophenol is synthesized by the direct chlorination of phenol and sold as the free phenol or as the sodium salt, sodium pentachlorophen-

ate. Commercial pentachlorophenol varies in purity with pentachlorophenol itself accounting for ~88-91% of the product. Analyses for two commercial (Dow) and one "purified" pentachlorophenol products are listed in Table II-2. No analyses of pentachlorophenol produced in the 1950s or earlier were found in the available literature. Manufacturing processes up to the middle 1950s were apparently based on a 1938 patent (Golumbic, 1953); manufacturing processes today appear to be based on patents issued in the late 1950s and early 1960s and purification methods patented in the 1970s (Freiter, 1979), so that the composition of pentachlorophenol may well have changed with time. In addition, pentachlorophenol appears to be a substantial component of commercial tetrachlorophenol (Schwetz et al., 1974a).

Summary

Pure pentachlorophenol has a molecular weight of 266.34, is a solid at ambient temperatures and forms colorless crystals with a phenolic odor. It has a water solubility of 14 mg/ℓ at 20°C and a pK_a of 4.74. Pentachlorophenol is stable in aqueous solution in the dark; however, photochemical (Wong and Crosby, 1981) and some microbial degradation (Alexander and Aleem, 1961; Baker et al., 1980; Tabak et al., 1981) will result in some depletion in surface waters. It has been found in finished drinking water and is known to persist in some surface waters, while degradation is apparent in others (Weyman and Hofstee, 1973; Weyman and van den Broek, 1980; Wong and Crosby, 1981).

TABLE II-2

Commercial Pentachlorophenol Impurities

	Dow Lot No. MM06210-9822[a]	Purified Ref. No. 29-91-1[a]	Unspecified Commercial[b]
Phenolics (%)			
Pentachlorophenol	88.4	98 +	90.4 ± 1.0
Tetrachlorophenol	4.4	0.27	10.4 ± 0.2
Trichlorophenol	<0.1	0.05	<0.1
Higher chlorinated phenoxyphenols	6.2	0.5	NR
Nonphenolics (ppm)			
2,3,7,8-Tetrachlorodibenzo-p-dioxin	<0.05	<0.05	<0.05
Hexachlorodibenzo-p-dioxin	4	<0.5	1.0 ± 0.1
Heptachlorodibenzo-p-dioxin	125	<0.5	6.5 ± 1.0
Octachlorodibenzo-p-dioxin	2500	<1.0	15.0 ± 3.0
Hexachlorodibenzofuran	30	<0.5	3.4 ± 0.4
Heptachlorodibenzofuran	80	<0.5	1.8 ± 0.3
Octachlorodibenzofuran	80	<0.5	<1
Hexachlorobenzene	NR	NR	400 ± 40

[a]Schwetz et al., 1974b

[b]Schwetz et al., 1978

NR = Not reported

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III. TOXICOKINETICS

Information on the toxicokinetics of pentachlorophenol in humans and animals after single doses is summarized in Table III-1. The available data indicate that pentachlorophenol is rapidly absorbed following acute oral, dermal or inhalation exposure, and then excreted over the next 3-6 days. The excretion rate may be reduced following chronic exposure.

Absorption

Oral Exposure. Meerman et al. (1983) examined the uptake of pentachlorophenol and sodium pentachlorophenol by male Wistar rats (100-120 g) after ad libitum exposures for 1 week in the diet or drinking water. Exposure levels, resultant plasma concentrations and other experimental details are presented in Table III-2. The investigators noted wide diurnal variations in plasma levels of pentachlorophenol associated with changes in feeding activity, with the highest plasma concentrations occurring during the night. Based on an analysis of plasma levels during a 24-hour period as well as toxicokinetic parameters obtained from a separate study using intravenous (i.v.) administration (Excretion Section), the investigators calculated that virtually all of the administered pentachlorophenol was absorbed from drinking water. Braun and Sauerhoff (1981) and Braun et al. (1977) compared the toxicokinetics of pentachlorophenol in rhesus monkeys and Sprague-Dawley rats. Groups of six rats, three of each sex, received a single gavage dose of 10 or 100 mg [^{14}C]pentachlorophenol/kg bw in 1 ml corn oil. Three male and three female monkeys, Macaca mulatta, weighing 3.3-4.9 kg received a single gavage dose of 10 mg/kg bw in 10 ml corn oil. In both species, pentachlorophenol was rapidly absorbed, with peak plasma levels occurring in 12-24 hours in the monkeys and 4-6 hours in the rats.

TABLE III-1

Pentachlorophenol Toxicokinetics in Mammals After Single Doses*

Species	Sex	Route (vehicle)	Dose (mg/kg)	Peak Blood Level (ppm)	Time to Peak Level (hours)	Half-Life (hours)	Excretion	Comments	Reference
Man	M	oral (NR)	0.1	0.248	4	30.2 (plasma)	Peak at 42 hours; half-life for PCP was 33 hours; half-life for PCP-glucuronide was 12.7 hours	74% in urine as PCP; 12% in urine as PCP-glucuronide; 4% in feces as PCP and PCP-glucuronide	Braun et al., 1978
Rat	M	oral (corn oil)	10	45 (plasma)	4-6	17 - α 40 - β (total body)	80% in urine, 19% in feces	Kinetic data on elimination of urinary metabolites not provided.	Braun et al., 1977
Rat	F	oral (corn oil)	10	45 (plasma)	4-6	13 - α 33 - β (total body)	78% in urine, 19% in feces	Same as above	Braun et al., 1977
Rat	M	oral (corn oil)	100	NR	NR	13 - α 121 - β (total body)	72% in urine, 24% in feces	Pooled urine of males and females: 75% as PCP; 9% as PCP-glucuronide; 16% as TCH. Half-lives were 24 hours for PCP, 25 hours for PCP-glucuronide, and 32 hours for TCH.	Braun et al., 1977
Rat	F	oral (corn oil)	100	NR	NR	27 (total body)	54% in urine 43% in feces	Same as above	Braun et al., 1977
Monkey	M	oral (corn oil)	10	10-30	12-24	72 (plasma)	Urine half-life 41 hours. 360 hours after single dose: 75% in urine; 12% in feces	In urine as unchanged PCP; no metabolites.	Braun and Sauerhoff, 1976
	F	oral (corn oil)	10	10-30	12-24	84 (plasma)	Urine half-life 92 hours; 360 hours after single dose: 70% in urine; 18% in feces; 11% remained in tissues.	Same as above	Braun and Sauerhoff, 1976
House	F	i.p. or s.c. (olive oil)	15-37	NR	NR	NR	72-83% excreted in urine in 4 days; about half in 24 hours; 5-7% in feces.	~45% as unchanged PCP; 14% as PCP conjugate; 40% as TCH.	Jakobson and Yllner, 1971

TABLE III-1 (cont.)

Species	Sex	Route (vehicle)	Dose (mg/kg)	Peak Blood Level (ppm)	Time to Peak Level (hours)	Half-Life (hours)	Excretion	Comments	Reference
Rat	NR	i.p. (olive oil or propylene glycol)	25	NR	NR	NR	70% in urine in 24 hours	43% as unchanged PCP; 5% as TCH; 38% as TCH conjugate; 14% as PCP conjugate.	Ahlborg et al., 1974
Mouse	NR	i.p. (olive oil or propylene glycol)	25	NR	NR	NR	70% in urine in 24 hours	41% as unchanged PCP; 24% as TCH; 22% as TCH conjugate; 13% as PCP conjugate.	Ahlborg et al., 1974

*Source: Modified from U.S. EPA, 1980

THC = Tetrachlorohydroquinone; NR = Not reported

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TABLE III-2

Uptake of Pentachlorophenol (PCP) or Sodium Pentachlorophenate (NaPCP) by Wistar Rats After a 1-Week Exposure in Food or Drinking Water[a]

	Number of Animals	Intake of PCP (μmols/kg/24 hours)	Body Weight After 1 Week[b]	Plasma Concentration of PCP[c] (μM)
Controls	4	0	128 ± 10	0
PCP in food (350 ppm)	4	190 ± 11	114 ± 9	30 ± 3
NaPCP in food (350 ppm)	5	200 ± 14	116 ± 10	36 ± 5
NaPCP in drinking water (1.4 mM) (~320 mg/ℓ)	4	162 ± 16	108 ± 9[d]	40 ± 8
Single dose of PCP (40 μmol/kg; i.p.) 60 minutes before harmol	4	40	128 ± 2	55 ± 4

[a]Source: Meerman et al., 1983

[b]The body weight of the animals at the start of the experiments was 94±1 g (mean ± S.E.M.; n = 17).

[c]Blood was taken from the rats at the end of the experiments, 4 hours after the administration of harmol. All values are expressed as means ± S.E.M.

[d]Significantly different from controls at $p<0.1$ (Wilcoxon's Test 21).

Absorption rate constants were not determined in rats. The average absorption half-time was 2.7 hours in monkeys.

Braun et al. (1978) compared the absorption of pentachlorophenol in man with the values previously determined for monkeys and rats. Four healthy male volunteers ingested a single dose of 0.1 mg pentachlorophenol/kg bw (vehicle not specified). The average half-time for absorption was found to be 1.3±0.4 hours.

Other Routes of Exposure. Casarett et al. (1969) investigated the absorption of pentachlorophenol by two groups of 11 workers at two wood-treating plants in Honolulu. Workers in these two plants had mean pentachlorophenol concentrations in the urine of 2.2 and 2.4 ppm/1000 milliosmoles based on monthly samples during a 1-year period. Corresponding values in a group of workers not involved in the commercial use of pentachlorophenol ranged from ~0.01-0.1 ppm/1000 milliosmoles. An examination of the wood-treating process suggested that the absorption of pentachlorophenol indicated by the elevated urinary concentrations could have been from inhalation or dermal routes or both. In an effort to determine the significance of inhalation exposure as a route of absorption, two subjects spent 45 minutes in an enclosed area during a process that resulted in mean ambient pentachlorophenol concentrations of 230 and 432 ng/ℓ for the two subjects, respectively. Based on measurements of respiratory rates during exposure, total recovered pentachlorophenol in the urine, and estimates of tidal volume, these investigators concluded that the two workers absorbed 88 and 76% of the total potential inhalation dose.

Distribution

A number of investigators have examined the tissue distribution of pentachlorophenol and its metabolites. Jakobson and Yllner (1971) administered 15 or 37 mg [^{14}C]pentachlorophenol/kg bw to female NMRI mice (20-30 g) by single subcutaneous (s.c.) or intraperitoneal (i.p.) injection. The dosing vehicle was olive oil. The highest concentrations of ^{14}C activity after i.p. treatment were found in the gall bladder, the wall of the stomach fundus, the contents of the gastrointestinal tract, and the liver. Lesser concentrations were detected in the kidneys, heart and brain. Only traces of ^{14}C were found in the lungs. Concentrations in other organs were not measured. A similar distribution of ^{14}C activity was found after s.c. treatment. Radioactivity was measured by liquid scintillation spectrometry after oxidation of tissues from mice treated intraperitoneally and by whole body autoradiography in mice treated subcutaneously.

Braun et al. (1977) found the highest levels of radioactivity in the liver and kidneys of Sprague-Dawley rats given a single oral dose of 10 mg [^{14}C]pentachlorophenol in corn oil/kg bw. The lowest tissue concentrations were detected in the brain and fat. Radioactivity was measured in different tissues and blood plasma taken from one male and one female at 4, 24, 48, 72 and 120 hours post-treatment. The distribution was qualitatively similar in both males and females; however, plasma concentrations during the elimination phase were higher in females than in males. In this study, the authors noted that tissue/plasma ratios and renal clearance rates were much lower than would be predicted, based on the octanol/water partition coefficient and glomerular filtration rate. This observation was explained by the affinity of plasma proteins for pentachlorophenol (molar binding affinity

constant = 10^6). In this study, ~99% of the plasma pentachlorophenol was bound to plasma proteins. In another experiment, Braun et al. (1977) recovered 0.315% and 0.045% of an oral dose of 10 mg [^{14}C]pentachlorophenol/kg from liver and kidney, respectively, removed from male and female Sprague-Dawley rats at 9 days following treatment. Larsen et al. (1972) reported a similar distribution pattern in tissues removed from male and female rats 40 hours after gavage treatment with 31-40 mg/kg of ^{14}C-pentachlorophenol in corn oil.

Grimm et al. (1981) analyzed tissues and body fluids removed at autopsy from 21 human subjects in Northern Bavaria. The causes of death were not related to pentachlorophenol exposure. The median urine level was 0.0044 µg pentachlorophenol/mℓ, with median blood levels of 0.023 µg/mℓ. The highest concentrations of pentachlorophenol residues (wet weight) were found in the liver (0.067 µg/g), kidney (0.043 µg/g), brain (0.047 µg/g), spleen (0.019 µg/g) and body fat (0.013 µg/g).

Bioaccumulation and Retention

Using a pharmacokinetic model, Braun and Sauerhoff (1976) have estimated the accumulation of pentachlorophenol in rhesus monkeys during repeated dosing (Table III-2). This estimate was based on pharmacokinetic coefficients obtained from a single-dose oral study in which groups of 3 males and 3 females were given 10 mg/kg bw. Corn oil was the dosing vehicle. They predicted that 99% of the steady-state plasma concentration (50 µg/g) would be reached in 20 days. This steady-state concentration is ~2-5 times the peak plasma levels observed following a single oral dose.

TABLE III-3

Theoretical Time (days) to Reach 30, 70, 90, 97 and 99% of the Steady-State Plasma Concentration of Pentachlorophenol Following Consecutive Daily Doses of 10 mg/kg Pentachlorophenol to Monkeys*

Dose	Percentage of Steady-State	Number of Days that Dose was Given	Approximate Plasma Concentration of PCP (µg/g)
10 mg/kg	30	2	15
	70	6	35
	90	10	45
	97	15	49
	99	20	50

*Source: Braun and Sauerhoff, 1976

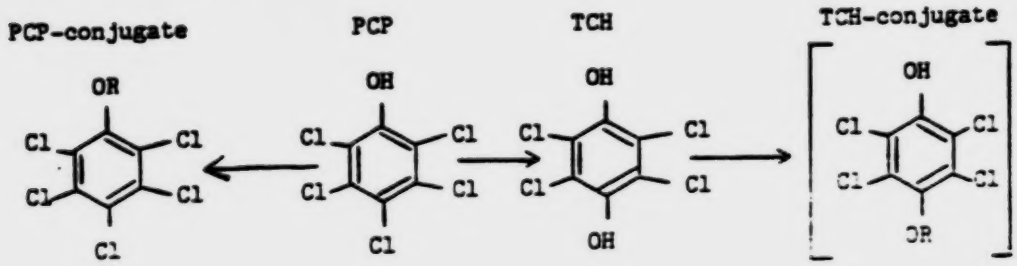
Using the same approach, Braun et al. (1978) also estimated the accumulation of pentachlorophenol in humans during repeated exposure. This estimate was based on a single-dose oral study in which four male volunteers ingested 0.1 mg pentachlorophenol/kg bw. A one-compartment open-system model with first-order absorption, enterohepatic circulation, and first-order elimination was used. Under these conditions, 99% of steady-state levels would be reached in 8.4 days. Predicted steady-state plasma concentrations (~0.5 µg/mL) were approximately twice those observed following a single dose.

Other studies, summarized in the Excretion Section, also indicate that the excretion kinetics of pentachlorophenol are appreciably altered by repeated exposure compared with single exposure. Consequently, it is difficult to develop models that describe chronic accumulation of pentachlorophenol based on pharmacokinetic coefficients obtained from acute studies.

Metabolism

Several investigators have studied the metabolism of pentachlorophenol in rats and mice. Jakobson and Yllner (1971) administered 15-37 mg [^{14}C]pentachlorophenol/kg bw to female NMRI mice by s.c. or i.p. injection. Less than 0.05% of the administered radioactivity was converted to $^{14}CO_2$ or other volatile metabolites. The urinary metabolites were identified by paper chromatography and isotope dilution techniques. Of the total urinary radioactivity, ~45% was found to be unmetabolized pentachlorophenol and the remainder to be conjugated compounds. When the urine was treated with 3N hydrochloric acid at 100°C for 1 hour before analysis in order to hydrolyze the conjugates, two labeled compounds were detected.

Pentachlorophenol (PCP) constituted ~60% of the total radioactivity. Tetrachlorohydroquinone (TCH) accounted for the remainder of the urinary radioactivity. Because of lack of material a reliable estimation of the amount of conjugated TCH could not be made. Based on these data, Jakobson and Yllner (1971) proposed the following metabolic pathway:



Similar results were obtained by Ahlborg et al. (1974) who determined the urinary metabolites of pentachlorophenol in NMRI mice and Sprague-Dawley rats when 10 or 25 mg [^{14}C]pentachlorophenol/kg bw was administered by i.p. injection or by gavage. Pentachlorophenol was dissolved in olive oil or propylene glycol. Total urinary radioactivity found to be unmetabolized pentachlorophenol was 41% for mice and 43% for rats. The major metabolite was identified as tetrachlorohydroquinone, accounting for 5% of the total urinary radioactivity in rats and 24% in mice. When the urinary conjugates were hydrolyzed by boiling with hydrochloric acid, all of the excreted radioactivity was present as pentachlorophenol (54% for mice and 57% for rats) and tetrachlorohydroquinone (43% for rats and 46% for mice). The mixed conjugates of pentachlorophenol and tetrachlorohydroquinone could not be identified as glucuronides, since the investigators found that tetrachlorohydroquinone was found to be a potent inhibitor of B-glucuronidase.

Braun et al. (1977) obtained similar results in Sprague-Dawley rats. Within 24 hours after a single 10 mg/kg dose by gavage, 48% had been excreted in the urine unchanged as pentachlorophenol, 10% as tetrachlorohydroquinone, and 6% as a PCP glucuronide conjugates. The isolated conjugate was extractable after the removal of PCP and TCH and the treatment with glucuronidase. The investigators speculated that the glucuronidase hydrolysis of the PCP glucuronide conjugate is apparently inactivated by tetrachlorohydroquinone.

Leighty and Fentiman (1982) have speculated that the in vivo retention of pentachlorophenol by lipid-containing tissues involves conjugation with fatty acids. They demonstrated the conjugation of pentachlorophenol with palmitic acid in an in vitro rat liver coenzyme A fortified microsomal system, but this conjugate has not been found in vivo.

Little is known of the metabolism of pentachlorophenol in humans. Ahlborg et al. (1974) analyzed the urine from two occupationally exposed spraymen 24 hours following exposure. The urine was hydrolyzed with concentrated hydrochloric acid, extracted with diethyl ether, methylated with diazomethane and analyzed by GC/MS. Both pentachlorophenol and tetrachlorohydroquinone were found (proportions not specified), indicating that metabolism of pentachlorophenol in humans is similar to that in rats and mice. This study provided no information on the existence of possible conjugated metabolites in human urine.

Excretion

Rodents. Jakobson and Yllner (1971) administered 15 or 37 mg [^{14}C]-pentachlorophenol/kg bw to female NMRI mice by s.c. or i.p. injection. Excretion was rapid, with approximately half of the total dose excreted during the first 24 hours. Most of the excreted radioactivity (72-83% in 4 days) was detected in the urine, ~6% was in the feces, and <0.05% was detected in the expired air. By 30 days postinjection, <1% of the dose remained in the mice.

Larsen et al. (1972) reported an analysis of the excretion kinetics of [^{14}C]pentachlorophenol in female rats (strain not specified) following a single oral dose (37-41 mg/kg bw). The urine was the major route of excretion, with 65.2% of the administered radioactivity recovered in the urine within 72 hours. Less than 0.04% of the administered radioactivity was detected in expired air. Urinary excretion was found to be biphasic, with half-lives of 10 hours and 102 days. The accuracy of these half-lives has been questioned on several points by Braun et al. (1977) who stated that unless total recovery of the dose, which was not reported by Larsen et al. (1972), is known to approach 100%, use of the sigma-minus plot by Larsen et al. (1972) might have caused gross errors in the estimation of elimination rates. Braun et al. (1977) noted that Larsen et al. (1972) did not consider fecal excretion in their calculations. For the purpose of their analysis, Larsen et al. (1972) assumed that fecal elimination was constant. Their analysis of pooled fecal samples collected throughout the 10-day collection period indicated elimination of 9.2-13.2% of the dose by this route.

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Biphasic elimination has also been reported by Braun et al. (1977). Single oral doses of 10 or 100 mg [^{14}C]pentachlorophenol/kg bw were administered to groups of 3 male and 3 female Sprague-Dawley rats. The urine was the major route of elimination, accounting for 80.11 and 78.13% of the dose in males and females, respectively, following administration of 10 mg/kg bw and 72.1% (males) and 54.4% (females) following a 100 mg/kg bw dose. The feces also contained high levels of radioactivity, accounting for 18.8% (males) and 19.3% (females) as well as 24.5% (males) and 42.8% (females) of the administered radioactivity following doses of 10 and 100 mg/kg bw, respectively. Expired air contained only 0.2% of the administered radioactivity following a dose of 10 mg/kg bw. Excretion in the expired air was not measured following the 100 mg/kg bw dose.

Biphasic elimination kinetics were observed in the male rats receiving either 10 or 100 mg [^{14}C]pentachlorophenol/kg bw and in females receiving 10 mg/kg bw. Elimination coefficients were calculated by a nonlinear parameter estimation program. The half-lives of the rapid phase of elimination were 17 and 13 hours for the male rats dosed with 10 and 100 mg/kg bw, respectively, and 13 hours for the female rats receiving 10 mg/kg bw. The corresponding half-lives for the slower phase of elimination were 40, 121 and 33 hours, respectively. More than 90% of the administered dose was eliminated during the rapid phase of excretion. Excretion in females receiving 100 mg/kg bw was monophasic with a half-life of 27 hours. The investigators offered no reason for the apparent first-order elimination process in the high-dose females; however, as described above, fecal and urinary elimination of ^{14}C was different in comparison with the other treatment groups.

Two factors appeared to contribute to the slow phase of elimination. The retention of radioactivity in the liver was considered to be the major contributor to the slow phase of elimination. At the latter time points, the liver contained ~70% of the total body burden of pentachlorophenol derived radioactivity. Also, as the plasma levels decreased, binding to the limited number of high-affinity sites on plasma proteins became a greater factor, reducing the renal clearance of pentachlorophenol.

Biphasic elimination was also observed in Wistar rats by Meerman et al. (1980), but the rates were greater than those observed in Sprague-Dawley rats. Sodium pentachlorophenate was administered intravenously, in contrast to oral dosing used in the studies with Sprague-Dawley rats, at a single dose of 40 μmol/kg (~10.6 mg/kg) as pentachlorophenol. The initial rapid phase of elimination had a half-life of 2.14 hours. The half-life of the slow phase of elimination was 7.24 hours.

Subhuman Primates. Braun and Sauerhoff (1976) administered a single oral dose of 10 mg [^{14}C]pentachlorophenol/kg bw to groups of 3 male and 3 female rhesus monkeys. Excretion was monophasic, with half-lives of 40.8 hours for males and 92.4 hours for females. As in rodents, the urine was the major route of excretion, accounting for 72-78% of the dose in males and 69-72% of the dose in females. Approximately 12% of the dose was excreted in the feces of males and 13-24% in females. The investigators suggested that the long biological half-lives observed were the result of extensive biliary excretion and enterohepatic recirculation.

The role of biliary excretion was further investigated by Ballhorn et al. (1981) and Rozman et al. (1982). Ballhorn et al. (1981) administered 30 or 50 mg [^{14}C]pentachlorophenol/kg bw to groups of two male rhesus monkeys each. After 24 hours, one monkey from each group was transfered to a diet containing 4% cholestyramine. This treatment increased fecal elimination by 9- to 14-fold and decreased urinary elimination by 2- to 6-fold. The authors concluded that cholestyramine interrupts the enterohepatic circulation of pentachlorophenol and its metabolites.

Rozman et al. (1982) repeated the studies of Ballhorn et al. (1981), using three male rhesus monkeys provided with a bile duct by-pass. Each monkey functioned as its own control. Monkeys were administered by gavage two doses of 50 mg/kg ^{14}C-pentachlorophenol 4 weeks apart. Twenty-four hours after the second dose of pentachlorophenol, 4% cholestyramine was added to the basal diet of each monkey for 6 consecutive days. Excretion was measured for 6 days after each dose. During the first 24 hours after dosing, excretion in the urine, feces and bile accounted for 20, 0.5 and 20% of the administered pentachlorophenol, respectively. Addition of 4% cholestyramine to the diet reduced urinary excretion during days 2-6 from 35 to 5% of the administered dose and increased fecal excretion from 3-54%. Total biliary excretion decreased from 70 to 52% of the dose. However, total excretion of the administered dose by the urine and feces was increased from 38-59% after cholestyramine treatment. The authors concluded that cholestyramine both interrupts enterohepatic recycling and increases the direct absorption of pentachlorophenol across the intestinal wall.

Human. Braun et al. (1978) orally administered 0.1 mg pentachlorophenol/kg bw to four male volunteers. They reported a plasma half-life of 30.2 hours. Within 168 hours, 74% of the administered dose had been eliminated in the urine as pentachlorophenol and 12% as pentachlorophenol-glucuronide. An additional 4% was excreted in the feces as pentachlorophenol and pentachlorophenol-glucuronide combined.

Bevenue et al. (1967a) measured the urinary levels of pentachlorophenol in 541 people (predominately male) in Honolulu and adjacent areas, 247 of which had some occupational exposure to the compound. Their data implied biphasic excretion kinetics. Urinary concentrations decreased 34.7%/day over the first 1-2 days following exposure, compared with 3.3%/day for 10-23 days following exposure and 0.85%/day for 64-115 days following exposure.

Casarett et al. (1969) used epidemiological methods to investigate the excretion of pentachlorophenol by workers in a wood-treating plant in Honolulu. The data indicated a possible difference in excretion kinetics between single high-level and chronic low-level exposures. Precise values were not reported. Following a single inhalation exposure, urinary excretion half-lives of 24 hours were observed in individuals; however, following chronic exposure the concentration decreased 60-80% when the workers were absent from work for up to 18 days. The authors postulated that this apparent difference in excretion kinetics between acute and chronic exposures may be attributable to a "... four compartment system for chronic inhalation exposure consisting of lung, plasma proteins, urine and tissue depots."

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Begley et al. (1977) determined pentachlorophenol concentrations in the blood and urine of 18 workers at a Honolulu wood-treating plant on the last day of work before a 20-day vacation, on days 3, 6, 13 and 20 of vacation, and on day 51 after they returned to work. Over the 20-day vacation period, blood and urine levels fell to <50% of the prevacation values. Interestingly, there was a slight rise in blood levels between days 3 and 6 of the vacation, possibly indicating mobilization of tissue depots. These data imply a urinary elimination half-time of 19-20 days for occupational exposure to pentachlorophenol.

Summary

The available data indicate that the biological handling of pentachlorophenol is similar across mammalian species. Pentachlorophenol is rapidly absorbed following oral, dermal or inhalation exposure. Once absorbed, pentachlorophenol is distributed throughout the body, accumulating in the liver, kidneys, brain, spleen and fat (Braun et al., 1977; Grimm et al., 1981; Jakobson and Yllner, 1971). The pentachlorophenol in the plasma is highly protein-bound, which greatly reduces the tissue/plasma concentration ratios and the renal clearance rate (Braun et al., 1977).

Pentachlorophenol appears [illegible] not readily metabolized since a large portion of the administered dose is excreted unchanged by all species tested. The major metabolic reactions of pentachlorophenol are conjugation to form the glucuronide and an oxidative dechlorination to form tetrachlorohydroquinone.

Based on a single dose study, Braun et al. (1978) predicted that steady-state levels would be reached in man within 8-9 days during chronic exposure. Under these conditions, maximum blood levels would be only about twice those observed following a single dose. Other investigators (Casarett et al., 1969; Begley et al., 1977) have reported half-lives for elimination of ~10 hours following an acute exposure, which is consistent with the value obtained by Braun et al. (1978); however, after chronic exposure, half-lives of ~20 days were reported. Pentachlorophenol may, therefore, have a greater potential for accumulation than the acute studies would indicate.

The major route of elimination is in the urine. The feces represents a minor route of excretion. Only trace amounts of metabolites have been detected in expired air. Biliary excretion occurs; however, extensive enterohepatic recirculation prevents this from being a major factor in the elimination of pentachlorophenol. Elimination is generally biphasic, with an initial rapid phase, followed by a period of much less rapid elimination. This pattern has been observed in rats (Braun et al., 1977) and man (Bevenue et al., 1967a), but not in subhuman primates (Braun and Sauerhoff, 1976).

IV. HUMAN EXPOSURE

This chapter will be submitted by the Science and Technology Branch, Criteria and Standards Division, Office of Drinking Water.

V. HEALTH EFFECTS IN ANIMALS

General Toxicity

Acute Toxicity. The acute toxicity of pentachlorophenol and sodium pentachlorophenate, as the LD_{50} or LD_{Lo}, are summarized in Table V-1. Following oral, i.p. or percutaneous administration, animals exhibit a rise in body temperature and respiration rate (McGavack et al., 1941; Deichmann et al., 1942; Farquharson et al., 1958). As coma develops, respiration becomes slower and dyspneic, with cardiac and muscular collapse and terminal asphyxial convulsive movements occurring near death. The onset of rigor mortis is immediate and pronounced. Other signs observed with varying frequency in pentachlorophenol poisoning include increased blood pressure, hyperglycemia and glycosuria, hyperperistalis and decreased urinary output. Most of the older studies and many of the more recent studies of acute toxicity used technical grade pentachlorophenol containing varying concentrations of chlorinated dibenzo-p-dioxins and dibenzofurans. In these studies, it is often impossible to differentiate the effects caused by pentachlorophenol from those caused by the contaminants.

Most of the information on the acute health effects of pentachlorophenol is based on two older studies by McGavack et al. (1941) and Deichmann et al. (1942). The chemical purity of the pentachlorophenol used by these investigators was not specified; thus, the degree to which chlorinated dioxins and dibenzofurans contributed to the observed results is unknown. The vehicle media used may also contribute to the toxicity of pentachlorophenol.

Deichmann et al. (1942) reported extensive vascular damage and heart failure in rats, rabbits, guinea pigs and dogs following a single oral

TABLE V-1

Acute Toxicity of Pentachlorophenol and Sodium Pentachlorophenate[a]

Compound	Route	Species	Dose Administered (mg/kg)	Response[b]	Reference
Pentachlorophenol	oral (fuel oil)	rats	27 (0.5% solution)	LD_{50}	Deichmann et al., 1942
	oral (olive oil)	rats	78 (1% solution)	LD_{50}	Deichmann et al., 1942
	oral	rats	30	LD_{50}	Deichmann, 1943
	oral	rats (male)	205	LD_{50}	Dow Chemical Co., 1969a
	oral	rats (female)	135	LD_{50}	Dow Chemical Co., 1969a
	oral	rats	50-140	LD_{50}	Meister, 1972
	oral	mice	74	LD_{50}	Ahlborg and Larsson, 1978
	oral	hamsters	168	LD_{50}	Cabral et al., 1979
	oral	rabbits	70	LD_{Lo}	Deichmann et al., 1942
	i.p.	rats	56	LD_{50}	Farquharson et al., 1958
	i.p.	rabbits	135	LD_{Lo}	Dittmer, 1959
	s.c.	rats	100	LD_{50}	Deichmann, 1943
	s.c.	mice	46	LD_{Lo}	BRL, 1968a
	s.c.	rabbits	70	LD_{Lo}	Deichmann et al., 1942

TABLE V-1 (cont.)

Compound	Route	Species	Dose Administered (mg/kg)	Response[b]	Reference
	s.c.	dogs	135	LD_{Lo}	Dittmer, 1959
	dermal	rats	105	LD_{50}	Noakes and Sanderson, 1969
	dermal	rabbits	40	LD_{Lo}	Deichmann et al., 1942
Sodium Pentachlorophenate	oral	rats	210.6	LD_{50}	Deichmann et al., 1942
	oral	rats	210	LD_{50}	Dow Chemical Co., 1969b
	oral	rabbits	275	LD_{50}	Dow Chemical Co., 1969b
	oral (aqueous)	rabbits	250-300 (5% solution)	LD_{Lo}	Deichmann et al., 1942
	oral	rabbits	550	LD_{Lo}	McGavack et al., 1941
	oral	guinea pigs	80-160	LD_{50}	Dow Chemical Co., 1969b
	i.p.	rats	30	LD_{50}	Hoben et al., 1976
	i.p.	rabbits	135	LD_{Lo}	McGavack et al., 1941
	s.c.	rats	80	LD_{50}	Deichmann et al., 1942
	s.c.	mice	56	LD_{Lo}	Dittmer, 1959
	s.c.	rabbits	100	LD_{Lo}	Deichmann et al., 1942
	s.c.	rabbits	275	LD_{Lo}	McGavack et al., 1941

TABLE V-1 (cont.)

Compound	Route	Species	Dose Administered (mg/kg)	Response[b]	Reference
	s.c.	dogs	135	LD_{Lo}	Dittmer, 1959
	i.v.	rabbits	22	LD_{Lo}	Deichmann et al., 1942
	inhalation	rats	11.7	LD_{50}	Hoben et al., 1976
	dermal	rabbits	250	LD_{Lo}	Deichmann et al., 1942
	dermal	rabbits	100-300 (20% solution)	LD_{50}	Dow Chemical Co., 1969b
	dermal	rabbits	512	LD_{Lo}	McGavack et al., 1941
	dermal	guinea pigs	266	LD_{Lo}	Dittmer, 1959

[a]Source: NIOSH, 1981

[b]LD_{50} = Dose lethal to 50% of recipients; LD_{Lo} = Lowest dose observed to cause lethality

administration of pentachlorophenol. Degenerative changes in the motor neurons and slight capillary congestion of the brain and spinal cord have been reported in rabbits that received a single oral dose of sodium pentachlorophenate (McGavack et al., 1941).

McGavack et al. (1941) and Deichmann et al. (1942) administered single dermal applications of a 10% sodium pentachlorophenate solution (60-600 mg/kg) to rabbits. At all doses, microscopic changes including widespread foci of atrophy and necrosis, thinning and disappearance of the upper skin layers, and irregular thickening (hyperkeratinization and hypertrophy of the hair follicles) at the site of treatment were observed. The subcutaneous layer underwent a gradual fibrillar thickening with hyaline degeneration following an initial period in which this layer became either thick and edematous or thin and flattened. Grossly, dermal exposure resulted in pronounced edema and inflammation with subsequent wrinkling, cracking, desquamation and loss of hair.

The acute effects of pentachlorophenol were studied by Nishimura et al. (1982) and Madge (1981). Nishimura et al. (1982) administered by gavage single doses of 0, 10, 30, 60, 120 or 150 mg sodium pentachlorophenate in water (>90% pure)/kg bw to male Wistar rats. The animals were sacrificed after 24 hours of fasting. All doses >10 mg/kg resulted in a significant ($p<0.01$) increase in liver wet weight/unit bw. Absolute liver weight and body weight data were not given. There was a dose-related increase in hepatic glycogen and lactate levels, with glycogen concentrations reaching levels >10-fold the control values, at doses of 120-150 mg/kg. No histological examinations were conducted.

Madge (1981) investigated the effect of pure and technical grade pentachlorophenol on intestinal absorption in the mouse. A single oral dose of 5 mg/kg bw technical grade pentachlorophenol was administered and, 7 days later, the intestine was removed and solute accumulation and solvent transfer were measured in vitro. Nonpurified grade pentachlorophenol decreased the absorption of D-glucose, apparently by increasing the rate of D-glucose metabolism. This effect was not observed after the administration of purified pentachlorophenol. Fluid transfer histology and small intestine wet weight was unaffected by either purified or technical grade pentachlorophenol treatment. Further details of the study were not available in the asbstract.

Chronic and Subchronic Toxicity. As with acute doses, much of our knowledge of the chronic and subchronic toxicity of pentachlorophenol is based on older studies using pentachlorophenol of undetermined purity.

Deichmann et al. (1942) investigated the effects of subchronic exposure in rats, cats and rabbits. No gross signs of toxicity were observed in groups of 10 rats fed diets containing 5 mg/rat/day pentachlorophenol for 26 weeks or 3.9 mg/rat/day for 28 weeks. Microscopic examination revealed unspecified histological abnormalities, which were not further described. Rats in both dose groups showed decreases in food consumption and body weight gain attributed by the authors to the unpleasant taste of the compound.

Deichmann et al. (1942) also administered daily gavage doses of 35 mg pentachlorophenol/kg bw as a 0.5% solution of the sodium salt to five rabbits for 15 consecutive days. Over the next 19 days, the daily dose was

gradually raised to 600 mg/kg bw. Death occurred following ingestion of a total of 1.9-3.9 g/kg bw. Blood concentrations at death ranged from 14-39 mg% compared with 8.5 mg% following a single lethal dose (LD_{50} data), indicating that a tolerance may develop following repeated administration of sublethal oral doses. In parallel experiments, no signs of toxicity as determined by blood and tissue concentrations were observed in a group of 23 rabbits that received daily gavage doses of 3 mg/kg bw, 6 day/week for a total of 90 doses or in groups of 4 cats that received diets equivalent to 1.25 or 2.5 mg/kg bw/day for 10 weeks.

Deichmann et al. (1942) also investigated the effect of subchronic (100 days) dermal administration of 41 mg sodium pentachlorophenate/kg bw in fuel oil to six rabbits for 6 days/week. They reported mild irritation, but no wrinkling, cracking or hair loss. Body weight gain was normal and there were no fatalities.

In parallel studies, Deichmann et al. (1942) investigated the subchronic to chronic dermal toxicity of pentachlorophenol to rabbits. Doses of 1-50 mg/kg bw as a 4% solution in fuel oil were applied to the dorsal skin once or twice a week for 6-61 weeks. The local effects observed were similar to those seen following the application of a single large dose (Acute Toxicity Section). A 2-3°F increase in rectal temperature was observed within 8 hours of the beginning of treatment and regularly thereafter with the increase in dosage levels. Though no specific symptoms were reported, 8 of the 20 rabbits treated died during the study. A dose-related increase in a number of unspecified gross and histological tissue changes was reported among the surviving rabbits.

In a series of experiments, McGavack et al. (1941) administered a solution of sodium pentachlorophenate of unknown purity subcutaneously, once a day for up to 60 days to groups of six rabbits. The doses used were 1/20, 1/10 or 1/4 of the minimum lethal dose (276 mg/kg). In the mid- and high-dose groups, death occurred after an average of 14.6 and 7.8 injections, respectively. There were no deaths in the low-dose group; however, 3 of the 6 rabbits exhibited signs of acute poisoning. In a parallel experiment, daily i.p. doses of 15 mg/kg produced death in an average of 11 days. Toxic symptoms for both the s.c. and i.p. routes were similar to those observed following acute intoxication. Death was accompanied by convulsive seizures that were less intense than those observed in acutely poisoned rabbits. Blood analysis revealed secondary anemia, leukopenia with relative lymphocytosis, polycythemia and increased blood sugar levels. Autopsy findings included hemorrhages and congestion in the lungs and kidneys, hypertrophy of the pulmonary artery, cloudy swelling of the liver and degenerative changes in the kidney tubules. Numerous lesions were observed in the brain and spinal cord, including capillary congestion, slight chromatolysis of nerve cells, diffuse focal areas of perivascular lymphocytic and mononuclear infiltration, and circumscribed subpial collections of unspecified small round cells.

Using technical grade pentachlorophenol reportedly containing 200 ppm octachlorodibenzo-p-dioxin and 82 ppm "preoctachlorodibenzo-p-dioxin", Knudsen et al. (1974) fed groups of 10 male and 10 female Wistar rats diets containing 0, 25, 50 or 200 ppm (0, 25, 50 or 200 mg/kg diet) pentachlorophenol for 12 weeks. Food consumption and behavior were normal throughout the treatment period; however, growth depression was noted in the female

rats receiving 200 mg/kg diets. Microsomal liver enzyme induction and increased liver weight were observed at dietary levels of 50 and 200 mg/kg diet. A dose-related decrease in calcium deposits in the kidneys of females was also observed (8/10 in controls, 2/10 in high-dose group). In this study, the NOEL was 25 mg/kg diet.

Mild but unspecified liver and kidney damage were reported in rats treated with 100 mg sodium pentachlorophenate/kg bw by daily gavage for 20 days (Dow Chemical Co., 1969a).

More recently, three groups of investigators compared the effects of subchronic administration of pure and technical grades of pentachlorophenol (Table V-2). Technical grade pentachlorophenol produced a number of effects that were not observed with the pure compound. These effects are consistent with contamination of the technical product by biologically active chlorinated dibenzo-p-dioxins and dibenzofurans.

Johnson et al. (1973) tested pure and technical grade pentachlorophenol in the chick edema bioassay, rabbit ear bioassay and a 90-day rat feeding study. The technical grade, but not the pure compound, produced positive results in both the chick edema assay and the rabbit ear assay (ie., chloracne). In the 90-day feeding study, Sprague-Dawley rats (number not specified) were fed diets resulting in a dose of 3, 10 or 30 mg/kg bw/day. Hematological changes including depression of erythrocytes, hemoglobin and packed cell values, and pathological changes consisting of focal hepatocellular degeneration and necrosis were reported with a dose of 30 mg technical grade pentachlorophenol/kg bw, while changes in clinical chemistry as well as increased liver weight and kidney weight were observed at all doses.

TABLE V-2

Subchronic Effects of Technical and Pure Pentachlorophenol on Rats*

Pentachlorophenol	Impurities	Dose and Duration of Study	Effects	Reference
Technical grade	1980 ppm octachlorodibenzo-p-dioxin 19 ppm hexachlorodibenzo-p-dioxin	3, 10 and 30 mg/kg/day in the feed for 90 days	Elevated serum alkaline phosphatase. Decreased serum albumin, hemoglobin and packed cell volume. Increased liver and kidney weights, with minimal focal hepatocellular degeneration and necrosis.	Johnson et al., 1973
Pure grade	No detectable chlorinated dioxins	3, 10 and 30 mg/kg/day x 90 days	Increased liver and kidney weights, but no gross or microscopic tissue changes.	Johnson et al., 1973
Improved technical	30 ppm octachlorodibenzo-p-dioxin 1.0 ppm hexachlorodibenzo-p-dioxin	3, 10 and 30 mg/kg/day x 90 days	Results similar to those obtained with pure pentachlorophenol.	Johnson et al., 1973
Technical grade	1380 ppm octachlorodibenzo-p-dioxin 520 ppm heptachlorodibenzo-p-dioxin 8 ppm hexachlorodibenzo-p-dioxin 260 ppm octachlorodibenzofuran 400 ppm heptachlorodibenzofuran 0 ppm hexachlorodibenzofuran 40 ppm pentachlorodibenzofuran 4 ppm tetrachlorodibenzofuran	20, 100 and 500 ppm in the diet x 8 months	Hepatic porphyria and increased hepatic aryl hydrocarbon hydroxylase and glucuronyl transferase activities, liver weight, cytochrome P-450 and microsomal heme. Decreased body weight at 500 ppm.	Goldstein et al., 1977
Pure grade	<0.1 ppm of all the above contaminants	20, 100 and 500 ppm in the diet x 8 months	No significant effect on the above parameters except glucuronyl transferase, which was increased at 500 ppm. Decreased body weight gain at 500 ppm which was comparable to that observed for the technical grade pentachlorophenol.	Goldstein et al., 1977
Technical grade	86% Purity. Analysis of impurities not reported.	50 or 500 mg/kg diet for 10-12 weeks	Increased incidence of methylcholanthrene-induced transplanted tumors. Increased mortality following primary Moloney sarcoma virus (MSV) inoculation and secondary challenge with MSV-transformed sarcoma cells (MSB). Depression of T-cell cytolytic activity. Enhanced macrophage phagocytosis.	Kerkvliet et al., 1982a,b
Pure grade	99+% Purity	50 or 500 mg/kg diet for 10-12 weeks	Enhanced splenic tumor development following MSV/MSB challenge.	Kerkvliet et al., 1982a,b

*Source: NIOSH, 1981

When pure pentachlorophenol was used, the only changes observed were increased kidney weight at the highest dose and increased liver weight at the two higher doses. In this study, 3 mg/kg/day represents a no effect level for pure pentachlorophenol based on increases in liver weights. Johnson et al. (1973) also tested an "improved" grade of pentachlorophenol, described in Table V-2, that produced results similar to those obtained with purified pentachlorophenol.

Goldstein et al. (1977) fed female Sherman rats (6/group) diets containing 0, 20, 100 or 500 ppm (0, 20, 100 or 500 mg/kg diet) pure or technical grade pentachlorophenol for 8 months, at which time survivors were sacrificed. The only reported effects of the pure compound was an increase in glucuronyl transferase and hepatic aryl hydrocarbon hydroxylase activities and decreased body weight at a dose of 500 mg/kg diet. In contrast, technical grade pentachlorophenol produced porphyria and increases in liver cytochrome P-450 at doses of 100 and 500 mg/kg diet and glucuronyl transferase induction. Also increased hepatic aryl hydrocarbon hydroxylase activity was observed at doses as low as 20 mg/kg diet.

Kerkvliet et al. (1982a,b) compared the immunotoxic effects of the pure and technical grades of pentachlorophenol. Male C57Bl/6 (B6) mice were maintained on diets containing 50 or 500 ppm (50 or 500 mg/kg diet) for 10-12 weeks before immune testing. The immune system was assessed by low-dose syngenic tumor transplant, Moloney sarcoma virus-induced tumor susceptibility, resistance to encephalomyocarditis virus infection, and allogenic sensitization for T-cell and macrophage activation.

No gross indications of toxicity were observed during the treatment period. Histological examinations revealed pathological changes only in the liver, with similar lesions resulting from exposure to both pure and technical grades of pentachlorophenol. There was a dose-related swelling of hepatocytes accompanied by nuclear swelling and vacuolization with eosinophilic inclusion bodies. Mild to moderate multifocal necrosis was observed in the high-dose group. Technical grade pentachlorophenol produced a dose-dependent delay and suppression of peak splenic antibody production and serum antibody titers. No decrease in humoral antibody response was observed in rats receiving purified pentachlorophenol. Pure pentachlorophenol did enhance the development of splenic tumors in mice challenged with Moloney sarcoma virus-induced tumor cells. The incidences of splenic tumor development following MSV/MSB challenges were 0, 22 and 44% in mice receiving 0, 50 and 500 mg pure pentachlorophenol/kg diet, respectively.

Additional studies of the effects of pentachlorophenol were performed by Schwetz et al. (1978), Greichus et al. (1979) and NTP (1989). Schwetz et al. (1978) fed diets resulting in a dose of 0, 1, 3, 10 or 30 mg purified pentachlorophenol/kg bw/day to groups of 27 male and 27 female Sprague-Dawley rats for 22 or 24 months, respectively. The pentachlorophenol used in this study was representative of Dowicide EC-7, a commercially available pentachlorophenol, and chemical analyses yielded the following composition based on four replicates: pentachlorophenol, 90.4±1.0%; tetrachlorophenol, 10.4±0.2%; trichlorophenol, <0.1%; 2,3,7,8-tetrachlorodibenzo-p-dioxin (DD), <0.05 ppm; hexachloro-DD, 1.0±0.1 ppm; heptachloro-DD, 6.5±1.0 ppm; octachloro-DD, 15.0±3.0 ppm; hexachlorodibenzofuran (DF), 3.4±0.4 ppm; heptachloro-DF, 1.8±0.3 ppm; octachloro-DF, <1; hexachlorobenzene, 400±40 ppm.

The pentachlorophenol used in this study is a purified grade since it has a lower content of contaminants than that found in technical grade pentachlorophenol. Changes in body weight, food consumption and overt behavior were recorded monthly. No data on mortality rates for the dose groups are provided. At the termination of the study, the observations made included hematology, clinical chemistry, urinalysis, organ weights and gross and microscopic examination of tissues. Decreased body weight gain was observed in females receiving 30 mg/kg bw/day (mean of 428 g in controls vs. 378 g in treated during last 12 months of the study). This dose also resulted in an increased urine specific gravity in females and increased serum glutamic pyruvic transaminase (SGPT) activity in both sexes (males-control 38±16, treated 63±13; females-control 36±8, treated 48±15). Pigmentation of the liver and kidneys was observed in females receiving 10 (8/27-liver, 7/29-kidney) or 30 (16/27-liver, 19/27-kidney) mg/kg bw/day and in males receiving 30 mg/kg bw/day (1/27-liver).

Greichus et al. (1979) administered oral doses of 0, 5, 10 or 15 mg purified pentachlorophenol/kg bw/day to four groups of six pigs for 30 days. Vehicle controls received daily capsules of pure lactose. Weight gain was measured weekly, blood chemistry values were determined at the beginning, middle and end of the study, and microscopic examinations were made on the liver, kidneys, spleen, brain and muscles at the end of the study. No differences in weight gain or feed consumption were observed in any of the groups. Liver weights were increased in the 10 and 15 mg/kg bw/day groups. The only histologic finding was a diffuse cloudy swelling of the hepatocytes in the treated pigs (specific groups not identified).

NTP (1989) administered various grades of pentachlorophenol to male and female B6C3F1 mice for either 30 days, 26-27 weeks or 2 years. The chemical compositions of these grades of pentachlorophenol are given in Table V-3. Criteria evaluated in these studies included food consumption, mortality, body weights, organ weights, hematology, clinical chemistry, urinalysis, hepatic enzyme induction, gross pathology and histopathology.

In the 30-day studies (NTP, 1989), groups of 5-15 female and 19 male mice were fed diets containing 0, 20, 100, 2500 or 12,500 ppm technical grade pentachlorophenol, Dowicide EC-7 or pure pentachorophenol. Compound-related deaths and decreases in body weight gain occurred at the highest dose (12,500 ppm) with EC-7 and pure pentachlorophenol (males only). Diffuse centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration and necrosis of the liver were compound-related lesions observed in all groups of animals that received any of the various grades of pentachlorophenol at 500 ppm and above.

In the 6-month studies (NTP, 1989), groups of 10 female and 10 male mice were fed diets containing either 200, 600 or 1800 ppm technical grade pentachlorophenol; 200, 600 or 1200 ppm DP-2; 200, 600 or 1200 ppm EC-7; or 200, 500 or 1500 ppm pure pentachlorophenol. Common control groups, fed unadulterated diets, consisted of 10 male and 10 female mice. All male mice that received 1800 ppm technical grade pentachlorophenol died before the end of the study, as did 2/10 male mice exposed to 1200 ppm DP-2. No compound-related clinical signs were observed at sublethal doses. All grades of pentachlorophenol caused increases in serum enzymes associated with liver injury. Absolute liver weights were significantly increased in all dosed groups, except in male mice receiving 200 ppm DP-2 or 1200 ppm EC-7.

TABLE V-3

Results of Chemical Analyses of Pentachlorophenol Used in the NTP (1989) 30-Day, 6-Month, and 2-Year Feed Studies[a,b]

Impurity	Pure	Technical Grade	DP-2	Dowicide EC-7[c]
Pentachlorophenol	98.6%	90.4%	91.6%	91%
Dichlorophenol	--	--	0.013%[d]	--
Trichlorophenol	<0.1%	0.1%	0.044%[e]	0.007%[f]
Tetrachlorophenol	1.4%	3.8%	7.0%[g]	9.4%
Hexachlorobenzene	10 ppm	50 ppm	15 ppm	65 ppm
Tetrachlorodibenzodioxin	<0.08 ppm	--	--	<0.04 ppm
Hexachlorodibenzodioxin	<1 ppm	10.1 ppm	0.59 ppm	0.19 ppm
Heptachlorodibenzodioxin	--	296 ppm	28 ppm	0.53 ppm
Octachlorodibenzodioxin	<1 ppm	1386 ppm	173 ppm	0.69 ppm
Pentachlorodibenzofuran	--	1.4 ppm	--	--
Hexachlorodibenzofuran	--	9.9 ppm	12.95 ppm	0.13 ppm
Heptachlorodibenzofuran	--	88 ppm	172 ppm	0.15 ppm
Octachlorodibenzofuran	--	43 ppm	320 ppm	--
Heptachlorohydroxydiphenyl ether	0.01%	0.11%[h]	0.05%[h]	
Octachlorohydroxydiphenyl ether	0.09%	1.91%	1.41%	--
Nonachlorohydroxydiphenyl ether	0.21%	3.56%	2.21%	--

TABLE V-3 (cont.)

Impurity	Pure	Technical Grade	DP-2	Dowicide EC-7[c]
Hexachlorohydroxydibenzofuran	0.11%	0.16%	0.07%	--
Heptachlorohydroxydibenzofuran	0.22%	0.47%	0.31%	--
Not quantitated	--	--	1/	--

[a]Adapted from NTP (1989)

[b]Samples were dissolved in benzene, placed on a deactivated alumina column, and eluted with benzene. Further separation was carried out with a basic aluminum oxide column; elution was with methylene chloride in hexane. Identification was performed by gas chromatography with an SP2100 capillary column/mass spectrometry; quantitation was by comparison with spiked samples analyzed by gas chromatography with an SP1240 DA column

[c]Four unidentified impurities with concentrations of 0.14, 0.057, 0.045 and 0.035 ppm were also detected.

[d]Probably the 2,4-isomer

[e]Probably the 2,4,6-isomer

[f]Identified as the 2,3,6-isomer; another isomer was believed to be present but was not identified.

[g]Probably the 2,3,4,6-isomer

[h]Includes octachlorodiphenyl ether

[i]Two isomers each of hexachlorohydroxybiphenyl and heptachlorohydroxybiphenyl were identified.

Relative liver weights were significantly increased for all dose groups of female mice, for all male mice that received technical grade pentachlorophenol, and for the mid- and high-dose groups of male mice that received EC-7, DP-2 or pure pentachlorophenol. A dose-related increase in spleen weight was observed in male mice exposed to all grades of pentachlorophenol; in contrast, a decrease in spleen weight was observed in female mice exposed to all grades of pentachlorophenol except pure.

In the 2-year studies (NTP, 1989), groups of 50 male and 50 female mice were fed diets containing 100 or 200 ppm technical grade pentachlorophenol or 100, 200 or 600 ppm EC-7 for 103 weeks. The average doses (provided by the authors) were ~17-18 or 35 mg/kg/day of technical grade pentachlorophenol or 17-18, 34-37 or 114-118 mg/kg/day of EC-7. No significant differences in survival rate were noted for either male or female mice exposed to either grade of pentachlorophenol. Compound-related nonneoplastic lesions occurred in the liver, spleen and nose of mice exposed to both grades of pentachlorophenol. The lesions observed in the liver included a dose-related increased incidence of clear cell foci, chronic active inflammation, pigmentation, necrosis, cytomegaly, proliferation of hematopoietic cells and bile duct hyperplasia. The effects were present at all dose levels. In the spleen a dose-related increase in diffuse hematopoietic cell proliferation in the red pulp was observed in the high-dose groups of male and female mice exposed to technical grade pentachlorophenol. In addition, acute focal inflammation of the mucosal glands was noted in the high-dose group of both sexes of mice exposed to EC-7.

Target Organ Toxicity

Based on the studies reported previously, the major target organs for systemic pentachlorophenol exposure appear to be the liver, kidneys and central nervous system. Dermal administration also results in toxic effects at the site of application.

Hepatic Effects. Pentachlorophenol appears to be an inducer of hepatic mixed-function oxidase. Vizethum and Goerz (1979) fed female Wistar rats diets containing 0.05% purified pentachlorophenol (500 mg/kg diet) for 2 weeks. This treatment resulted in a statistically significant ($p<0.05$) increase of both the content and activity of cytochrome P-450 in microsomes and the nuclear membranes.

Technical grade pentachlorophenol has been demonstrated to produce a variety of hepatic effects. Fleischer et al. (1980) administered 30 mg technical grade pentachlorophenol/kg bw/day to male Wistar rats for 15 consecutive days by i.p. injection. The livers were excised and examined by light and electron microscopy 24 hours after the last injection. Light microscopy revealed enlargement of the sinusoids accompanied by activation of the Kuppfer cells, a larger heterochromatin/euchromatin ratio, and an increase in the number of nucleoli in the hepatocytes (20.59%, $p<0.001$). At the level of the electron microscope, mitochondria were found to be reduced in size and pleomorphic. Occasional swelling and clearing of the matrix and cristolysis were seen. There was a pronounced proliferation of the smooth endoplasmic reticulum, with the greatest increase occurring around the bile canaliculi.

Purified pentachlorophenol appears to produce less severe hepatic effects than does the technical grade. Kimbrough and Linder (1978) investigated the effects of technical and purified pentachlorophenol on rat liver. Diets containing 0, 20, 100 or 500 ppm (0, 20, 100 or 500 mg/kg diet) were fed to Sherman rats for 8 months. At a dietary concentration of 500 ppm, purified pentachlorophenol resulted in slightly enlarged liver cells with occasional eosinophilic cytoplasmic inclusions. Technical grade pentachlorophenol produced such alterations in hepatic morphology at all doses tested.

Schwetz et al. (1978) fed male and female Sprague-Dawley rats for up to 24 months on diets that resulted in doses of 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day. The specific composition of the compound is presented at the end of the General Toxicity Section. In the two high-dose groups, a dose-related incidence of dark discolored livers were noted at necropsy. Microscopic examination revealed brown granular pigment within hepatocytes and reticuloendothelial cells surrounding the central vein in 1/27 livers from the high-dose males, 8/27 livers from females receiving 10 mg/kg bw/day and 16/27 livers from females receiving 30 mg/kg bw/day.

In the NTP (1989) studies, described in more detail in the previous section, a variety of hepatic effects were observed in B6C3F1 mice fed diets containing various grades of pentachlorophenol. In the 30-day studies, diffuse centrilobular cytomegaly, karyomegaly, nuclear atypia, degeneration and necrosis of the liver were compound-related lesions observed in all groups that received pure pentachlorophenol, technical grade pentachlorophenol or EC-7 at $\geq$500 ppm. Increases in mean serum glutamic pyruvic transaminase

values were observed for all male and female mice that were exposed to pentachlorophenol. Induction of liver aryl hydrocarbon hydroxylase activity and increased P-450 levels were observed after exposure to each of the three grades of pentachlorophenol, with technical grade pentachlorophenol being the most potent inducer. Pure pentachlorophenol, especially at higher concentrations, decreased the phosphate:oxygen ratio, indicating an uncoupling effect on oxidative phosphorylation.

In the 6-month studies (NTP, 1989), technical grade pentachlorophenol, DP-2, EC-7 and pure pentachlorophenol all caused increases in serum enzymes associated with liver injury. All grades of pentachlorophenol also resulted in a dose-related increase in liver weight. A dose-related induction of aryl hydrocarbon hydroxylase activity was observed with all grades of pentachlorophenol. Although this inductive effect was largely attributed to dibenzodioxin and dibenzofuran impurities in the various grades of pentachlorophenol, it was deemed likely that the small inductive effect observed with pure pentachlorophenol was due to pentachlorophenol itself. Furthermore, histopathologically observable liver lesions were present at all doses with all four grades of pentachlorophenol, but were less severe at comparable doses in mice exposed to pure pentachlorophenol; the lesions consisted of hepatocellular karyomegaly, cytomegaly and degeneration.

Liver lesions observed in the 2-year studies with technical grade pentachlorophenbol and EC-7 included a dose-related increased incidence of clear cell foci, chronic active inflammation, pigmentation, necrosis, cytomegaly, proliferation of hematopoietic cells and bile duct hyperplasia.

Since inhibition of cellular respiration is believed to be a major mechanism by which pentachlorophenol induces its toxic effect (see the Uncoupling of Oxidative Phosphorylation Section in Chapter VII), Gotz et al. (1980) investigated the effect of purified pentachlorophenol on cellular respiration and transport of sulfobromophthalein in isolated rat hepatocytes. At concentrations of 4 μM or more, pentachlorophenol inhibited the secretion of the sulfobromophthalein-glutathione conjugate. At a concentration of 5 μM, mitochondrial respiration was completely uncoupled.

Renal Effects. Johnson et al. (1973) maintained Sprague-Dawley rats on diets that provided 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day for 90 days. Purified pentachlorophenol produced increases in kidney and liver weight at a dose of 30 mg/kg bw/day. Commercial grade pentachlorophenol produced increases in kidney weight at doses as low as 3 mg/kg bw/day.

Schwetz et al. (1978) examined the histological effects of Dowicide EC-7 antimicrobial, a purified grade pentachlorophenol, on kidney tissue. Groups of 27 male and 27 female Sprague-Dawley rats were maintained on diets that provided 0, 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day for 22-24 months. A dose-related incidence (7/27 in 10 mg/kg group; 19/27 in 30 mg/kg group) of an unidentified brown granular pigment was observed within the tubular epithelial cells of the females.

Central Nervous System Effects. The central nervous system appears to be a major target for pentachlorophenol toxicity. McGavack et al. (1941) administered s.c. doses of 1/20, 1/10 or 1/4 of the minimum lethal dose (276 mg/kg bw) of pentachlorophenol (purity unspecified) daily for up to 60

days. A number of central nervous system lesions were observed in all dose groups, including capillary congestion, slight chromatolysis of nerve cells, diffuse focal areas of perivascular lymphocytic and mononuclear infiltration, and circumscribed subpial collections of unspecified small round cells. Gross symptoms (muscular weakness and convulsive seizures) observed following a lethal dose of pentachlorophenol are also consistent with toxic effects on the nervous system.

Other Effects

Carcinogenicity. Commercial grade pentachlorophenol, Dowicide-7, has been tested for carcinogenicity in (C57Bl/6 x C3H/Anf)F_1 and (C57Bl/6 x AKR)F_1 mice (BRL, 1968a). For each strain, groups of 18 male and 18 female mice were administered 46.4 mg pentachlorophenol/kg bw/day by gavage from day 7-28 postpartum. The mice were then transfered to diets containing 130 ppm (130 mg/kg diet) pentachlorophenol for the next 78 weeks. Survival was ~50% in all treated groups. Controls consisted of 79-90 mice of each sex and strain, which had either been untreated or had received only the carrier, gelatin. In the same study, identical groups of mice were administered single s.c. injections of 46.4 mg pentachlorophenol/kg bw in corn oil at age 28 days. There were no statistically significant differences in tumor incidence between treated and control groups.

Schwetz et al. (1978) investigated the carcinogenicity of a commercial grade of pentachlorophenol (described in the Chronic and Subchronic Toxicity Section) in Sprague-Dawley rats. Groups of 27 rats of each sex were fed diets containing pentachlorophenol at concentrations that resulted in doses

of 0, 1, 3, 10 or 30 mg/kg bw/day for a total of 22-24 months. No significant increase in total or specific types of tumors was found when the treated animals were compared with controls. Survival between groups was similar.

Catilina et al. (1981) tested both purified and technical grades of pentachlorophenol (6 mg/kg bw/dose) for carcinogenicity in Wistar rats. The pentachlorophenol was administered by s.c. injection, 3 times/week for 40 weeks. No evidence of carcinogenicity was observed after a 30-month, post-treatment observation period; however, transient alterations in white blood cell counts (depressed cell counts) were noted in the groups receiving purified pentachlorophenol.

Recently, NTP (1989) completed a 2-year carcinogenisis study of two grades of pentachlorophenol (technical grade and EC-7) in B6C3F1 mice. Analysis of impurities in these preparations is given in Table V-3. Technical grade pentachlorophenol was administered daily in the feed at dose levels of 100 and 200 ppm (17-18 and 35 mg/kg/day) to groups of 50 male and 50 female mice for 103 weeks. Two groups of control mice (35/sex) were fed basal diets. The incidences of hepatocellular adenomas and/or carcinomas in mice fed technical grade pentachlorophenol were significantly increased in male mice when compared with controls (control = 7/32, 100 ppm = 26/47, 200 ppm = 37/48). The incidences of benign and malignant pheochromocytomas of the adrenal medulla were also significantly greater in male mice than in controls (control = 0/31, 100 ppm = 10/45, 200 ppm = 23/45). There was no significant increase in liver tumors or pheochromocytomas in female mice. Vascular tumors (hemangiomas and/or hemangiosarcomas) were observed in

female mice, but not in male mice. The hemangiosarcomas were statistically significant when compared with controls (control = 0/30, 100 ppm = 3/48, 200 ppm = 6/46) and all were malignant.

EC-7 pentachlorophenol was administered daily in the feed at dose levels of 100, 200 and 600 pppm (NTP, 1989). The average daily doses of EC-7 were approximately 17-18, 34-37 and 114-118 mg/kg, respectively. Two groups of control mice were fed basal diets. The incidences of hepatocellular adenomas and/or carcinomas were significantly increased in male mice exposed to EC-7 when compared with controls (control = 6/35, 100 ppm = 19/48, 200 ppm = 21/48, 600 ppm = 34/39). The incidences of benign and malignant pheochromocytomas of the adrenal medulla in males were also significantly greater than in controls (control = 1/34, 100 ppm = 4/48, 200 ppm = 21/48, 600 ppm = 45/49). Furthermore, there was a significant increase in liver tumors (control = 1/34, 100 ppm = 4/50, 200 ppm = 6/49, 600 ppm = 31/48) and benign and malignant pheochromocytomas in female mice at the highest dose only (control = 0/35, 100 ppm = 2/49, 200 ppm = 2/46, 600 ppm = 38/49). Vascular tumors (hemangiomas and hemangiosarcomas) were observed in female mice but not in male mice. The incidence of hemangiosarcomas was statistically significant when compared with controls (control = 0/34, 100 ppm = 1/50, 200 ppm = 3/48, 600 ppm = 9/47) and all but one of the tumors was malignant.

In an initiation/promotion study, commercial grade pentachlorophenol was not found to be a promotor of skin carcinogenesis (Boutwell and Bosch, 1959). A single application of 75 µg DMBA (0.3% in benzene) was applied to the backs of thirty-five 2- to 3-month-old Sutter mice. After a 1-week

recovery period, twice weekly applications of 25 µg pentachlorophenol in benzene were begun and continued for 14 weeks. The mice were then observed for the remainder of the 24-month study. No promotion of tumor development was detected.

Mutagenicity. The mutagenicity of pentachlorophenol in prokaryotic organisms is summarized in Table V-4. In a large number of assays, pentachlorophenol failed to produce mutations in Salmonella typhimurium, Escherichia coli or Serratia marcescens, either with or without activation by mammalian S-9 mixtures.

Fahrig (1974) and Fahrig et al. (1978) reported positive results for the induction of forward mutations in Saccharomyces cerevisiae at concentrations as low as 0.19 mM (50 mg/L). Negative results were obtained when intragenic or intergenic recombination were used as the endpoints.

Positive results have also been obtained in the Bacillus subtilis rec assay (Shirasu, 1976; Waters et al., 1982). Shirasu (1976) reported weakly positive results using strains H17Rec$^+$ and M45Rec$^-$ with a dose of 5 µg/plate. Waters et al. (1982) tested six unspecified concentrations, with a maximum concentration of 10 mg/plate. Positive results were obtained, but no information on dose-response was reported.

In other in vitro tests, pentachlorophenol produced a slight increase in chromosomal aberrations in human lymphocytes (Fahrig, 1974). The test system used by Fahrig is only capable of detecting short-term effects; therefore, based on the data presented in the report, the statistical significance of this increase cannot be determined.

TABLE V-4

Mutagenicity of Pentachlorophenol in Unicellular Organisms

Type of Test	Species	Strain	Dose	Purity	Result	S-9	Comments	Reference
Spot	S. typhimurium	8 NS	NA	commercial	-	-		Andersen et al., 1972
Spot	S. typhimurium	LT-2	NA	NS	-	-		Lemma and Ames, 1975
Liquid suspension	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	NS	NS	-	+/-		Simmon et al., 1977
Vapor	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	NA	NS	-	+/-		Simmon et al., 1977
Plate incorporation	S. typhimurium	TA100, TA98, TA1535, TA1537 and TA1538	up to 5 mg/plate	commercial	-	+/-		Moriya et al., 1983
Plate incorporation	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	up to 10 mg/plate	technical	-	+/-		Waters et al., 1982
Plate incorporation	S. typhimurium	TA1535, TA1537, TA1538, TA98 and TA100	up to 5 mg/plate	NS	-	+/-		Simmon et al., 1977
Plate incorporation	S. typhimurium	TA98, TA100 TA1535, TA1537	up to 30 µg/plate	technical	-	+/-		NTP, 1989
Host mediated	S. typhimurium	G46	NS	NS	-	NA		Buselmaier et al., 1973
Host mediated	S. marcescens	a21	NS	NS	-	NA		Buselmaier et al., 1973
Spot	S. marcescens	a21, a742	NA	NS	-	-		Fahrig, 1974
Plate incorporation	E. coli	WP2uvr⁻	up to 5 mg/plate	NS	-	+/-		Simmon et al., 1977
Liquid suspension	E. coli	NS	NS	NS	-	-		Fahrig, 1974
Plate incorporation	E. coli	WP2hcr	up to 5 mg/plate	NS	-	+/-		Moriya et al., 1983

10/10/90

TABLE V-4 (cont.)

Type of Test	Species	Strain	Dose	Purity	Result	S-9	Comments	Reference
Plate incorporation	E. coli	WP2uvrA	up to 10 mg/plate	technical	-	+/-		Waters et al., 1982
Spot	E. coli	p3478, W3100	up to 10 mg	technical	-	-		Waters et al., 1982
Rec	B. subtilis	M45, H17	up to 10 mg/plate	technical	+	-		Waters et al., 1982
Rec	B. subtilis	H17Rec+, M45rec-	5 µg/plate	NS	±	-	Weakly positive results	Shirasu, 1976
Liquid suspension	S. cerevisiae	D3	NS	NS	-	+/-		Simmon et al., 1977
Liquid suspension	S. cerevisiae	MP-1	400 mg/l	purified	+	-	Positive for forward mutation, negative for intragenic and intergenic recombination	Fahrig et al., 1978
Liquid suspension	S. cerevisiae	aAeZ, trp5	0.19 mM	NS	+	-		Fahrig, 1974

NA = Not applicable; NS = Not specified

Pentachlorophenol was weakly positive for induction of sister chromatid exchanges in CHO cells within a dose range of 3-30 µg/mL only in the absence of S9 (NTP, 1989). Conversely, in the test for chromosomal abberation induction, pentachlorophenol gave a positive response only in the presence of S9; with significant increases in abnormal metaphases at doses of 80 and 100 µg/mL.

Pentachlorophenol has also been tested for mutagenicity in the Drosophila melanogaster sex-linked recessive lethal test (Fahrig, 1974; Fahrig et al., 1978; Vogel and Chandler, 1974). The concentration used was not specified in the studies by Fahrig et al. (1978), but Vogel and Chandler (1974) used a concentration of 7 mM in the media. No increase in sex-linked recessive lethals was reported in either study.

Only one study has been reported in which the mutagenicity of pentachlorophenol was tested in a mammalian species. Fahrig et al. (1978) bred female C57Bl/6JHan mice to fertile males of a rotation bred T-stock, yielding embryos that were heterozygous for four different coat-color genes. On day 10 of gestation, the dams were administered a single i.p. injection of either 50 or 100 mg purified pentachlorophenol/kg bw. The pups were checked for color spots twice a week between the ages of 2 and 5 weeks postpartum. Under these conditions, 9/473 pups evidenced color spots in their fur, 4 of which were considered to be definite indications of mutation. One gray color spot and one light brown color spot were observed in the 50 mg/kg dose group. One light gray and one gray color spot were seen in the 100 mg/kg group. In the controls, only 1/967 pups had a color spot definitely resulting from mutation. Fahrig et al. (1978) concluded these changes were evidence of definite but weak mutagenic activity.

Only limited information is available on the in vivo mutagenicity of pentachlorophenol in humans. Wyllie et al. (1975) investigated the induction of chromosomal aberrations in workers at a wood-treatment plant in Idaho. During the 5-month study period, the average monthly air concentrations ranged from 263.0-1887.9 ng/m³. Peripheral blood cells were cultured and 25 cells from each culture (6 exposed, 4 control samples) were scored for chromosome number, abnormal configurations, breaks and gaps. No statistically significant differences were observed between control and exposed groups; however, the number of breaks and gaps was consistently higher in exposed groups as compared with control groups.

Teratogenicity. A number of investigators have studied the teratogenicity of pentachlorophenol in rats. Larsen et al. (1975) investigated the teratogenicity of purified pentachlorophenol (60 mg/kg bw) in CD rats (6 dams/group). A single dose was administered by gavage on day 8, 9, 10, 11, 12 or 13 of gestation. The incidence of resorptions in the treated groups was not significantly greater than that in controls. The authors concluded that the number of rats with malformations (4) was minimal and could have been due to maternal toxic effects; however, 3 (exencephaly, micropnthalmia, and absent tail) of the 4 observed malformations occurred in litters exposed on day 9 of gestation. The fourth, dwarfism, occurred in a rat exposed on day 8. Treatment on day 9 or 10 of gestation also resulted in a significant ($p<0.05$) reduction in fetal weight gain (20 and 13%) with the greatest reduction occurring following treatment on day 9.

Schwetz and Gehring (1973) and Schwetz et al. (1974b) administered daily oral doses of both commercial (88% pure) and purified (>98% pure)

pentachlorophenol in corn oil to 20 Sprague-Dawley rats per group on days 6-15 of gestation at doses of 0, 5, 15, 30 and 50 mg/kg/day. The maximum tolerated dose to dams in these studies was 50 mg commercial pentachlorophenol/kg bw/day. A dose-related fetotoxicity ($p<0.05$ increased number of resorptions in each treated group, decreased fetal body weight with the two top doses, increased incidences of subcutaneous edema, skeletal anomalies in fetuses in the two top dose groups and increased incidence of dilated ureters in fetuses in the top dose group) was reported. Maternal body weight gain was lower ($p<0.05$) with the two highest doses. The purified pentachlorophenol was slightly more toxic as evidenced by effects on maternal weight gain (significant $p<0.05$ decreases in the top two dose groups), fetal body weight and crown-rump length ($p<0.05$ decrease with the high dose), fetal anomalies and resorptions (increased $p<0.05$ in the two top dose groups) than the commercial product. The authors included anomalies of the skull, ribs, vertebrae and sternebrae as well as subcutaneous edema, all of which were increased ($p<0.05$) in the highest dose groups, as signs of fetotoxicity rather than teratogenicity. Delayed ossification of the fetal skull was also increased ($p<0.05$) in incidence at the 5 mg/kg and 15 mg/kg purified pentachlorophenol levels. The sex ratio of the surviving pups was significantly ($p<0.05$) altered by a dose of 50 mg commercial pentachlorophenol/kg bw/day, M:F of 79:21, and a dose of 30 mg purified pentachlorophenol/kg bw/day, M:F of 83:17. Additional groups of rats were given corn oil alone or 30 mg/kg of either commercial or purified pentachlorophenol in corn oil on gestation days 8 through 11 or 12 through 15. The fetus was more suscep- tible to the toxic action of pentachlorophenol (both commercial and purified) during early organogenesis (days 8-11). Both pentachlorophenol products induced decreased ($p<0.05$) maternal weight gain and

increased ($p<0.05$) incidences of subcutaneous edema and skeletal anomalies in fetuses exposed during gestation days 8-11. Purified pentachlorophenol also increased ($p<0.05$) the incidence of resorptions when given on days 8-11 and subcutaneous edema and sternebral anomalies when given on days 12-15. Commercial pentachlorophenol also increased ($p<0.05$) the incidence of fetal skeletal anomalies. Fetal body weight and crown-rump length were decreased ($p<0.05$) when both products were given on days 8-11 and when purified was given on days 12-15.

Based on the above results the authors concluded that 5 mg/kg bw/day was a NOEL for the commercial grade of pentachlorophenol. However, the conclusion in the U.S. EPA Position Document 4 (U.S. EPA, 1984) is that this study did not establish a fetotoxicity NOEL for either grade of pentachlorophenol, since 5.0 mg/kg/day purified pentachlorophenol produced delayed skull ossification in the same study.

Larsen et al. (1975) administered a single oral dose of uniformly labeled [^{14}C]pentachlorophenol (60 mg/kg bw) to CD rats on day 15 of gestation. Analysis of radioactivity indicated that only negligible amounts of pentachlorophenol crossed the placental barrier. These data, combined with the observation that treatment on days 9 and 10 of gestation resulted in the greatest effects on rats, indicate that transport by the yolk-sac may be a significant factor in the fetotoxic response of rodents to pentachlorophenol.

One study has been reported in which the teratogenicity of pentachlorophenol in mice was assayed (BRL, 1968b). Commercial pentachlorophenol,

Dowicide-7, was tested for teratogenicity in six litters of BL6 mice. A dose of 25 mg/kg bw in dimethylsulfoxide was administered by s.c. injection on days 6-14 of gestation. No increases in fetal mortality or terata were reported in this study.

The only other species in which pentachlorophenol has been tested for teratogenicity is the Golden Syrian hamster (Hinkle, 1973). Daily oral doses of 1.25-20 mg pentachlorophenol (purity unspecified)/kg bw/day were administered on days 5-10 of gestation. An increase in fetal deaths and resorptions (or both) were reported in 3/6 test groups; however, no details were given in the abstract. A more detailed publication of this study has not been encountered in the literature.

Two groups have studied the effects of longer-term exposures on reproductive function and fetal development. Schwetz et al. (1978) fed groups of 10 male and 20 female Sprague-Dawley rats on diets that resulted in a dose of 0, 3 or 30 mg pentachlorophenol kg bw/day (described in the Chronic and Subchronic Toxicity Section) for 62 days before mating, during the mating period and throughout gestation and lactation. A dose of 3 mg/kg bw/day produced no measurable effect; however, a dose of 30 mg/kg bw/day resulted in a significant ($p<0.05$) reduction in neonatal body weight over the 21-day observation period (75% of controls at day 21), a decreased percentage of live births (93% of controls, $p<0.05$), and decreased survival of the pups at days 7, 14 and 21 (80% of controls at day 21). The significant increase ($p<0.05$) in lumbar spurs and vertebrae with unfused centra in high-dose litters was attributed to perinatal toxicity. The 30 mg/kg bw/day dose also resulted in a significant decrease (90% of controls $p<0.05$) in maternal body

weight on day 21 postpartum indicating that maternal toxicity may have influenced the fetotoxic effects observed.

Exon and Koller (1982, 1983a,b) fed groups of 12-20 female SprageDawley rats on diets containing 0, 5, 50 or 500 ppm (0, 5, 50 or 500 mg/kg diet) pentachlorophenol (95% purity by manufacturer; reanalysis indicated 85.5% purity) from weaning at 21 days of age through breeding at 90 days and continuing until the pups were weaned at 3 weeks postpartum. Some of the pups were continued on pentachlorophenol-containing diets for an additional 10 weeks. The study was designed to produce offspring that were exposed to pentachlorophenol both prenatally and postnatally. During the third trimester of pregnancy, rats were administered precursors of a known carcinogen, ethylnitrosourea (ENU). A dose-related but not statistically significant increase in conception rate was observed in all treatment groups. Pentachlorophenol produced significant effects (data were not presented) on the immune system in the progeny, as indicated by decreased antibody titers, decreased delayed-type hypersensitivity and increased peritoneal macrophage numbers. Pentachlorophenol also reduced the latency of ENU-induced transplacental carcinogenesis when compared with the ENU-induced only group. No statistically significant effects were observed on red or white blood cell counts, packed cell volume, hemoglobin levels, mean corpuscular volume, litter size, birth weight, weight at weaning or survival to weaning.

Summary

Acute exposure of experimental mammals to pentachlorophenol results in an initial rise in body temperature and respiration rate. Respiration then becomes slower and dyspneic as coma develops. Death is characterized by

cardiac and muscular collapse with terminal asphyxial convulsions. An immediate and pronounced rigor mortis is often noted. Oral LD_{50}s ranging from 27 to >300 mg/kg bw have been reported (see Table V-1), with no species being noticeably more susceptible than any other. The lower LD_{50} values tend to be found in the older literature and probably reflect a high degree of contamination by chlorinated dibenzo-p-dioxins and dibenzofurans. There are indications that tolerance to pentachlorophenol toxicity develops with prolonged exposure to the compound (Deichmann et al., 1942).

A wide variety of symptoms have been reported following subchronic oral administration (60 days) of pentachlorophenol, including secondary anemia, leukopenia, polycythemia, increased blood sugar levels, increased liver and spleen weights, increased serum enzymes associated with liver injury, heart dilation, hemorrhages and congestion in the lungs and kidneys, hypertrophy of the pulmonary artery, liver lesions, degenerative changes in the kidney tubules, and numerous lesions of the brain and spinal cord (McGavack et al., 1941; NTP, 1989). Dermal application also results in local irritation (Deichmann et al., 1942). Commercial pentachlorophenol containing chlorinated dibenzo-p-dioxins and dibenzofurans has been shown to be more toxic than purified pentachlorophenol in recent subchronic animal studies (Goldstein et al., 1977; Johnson et al., 1973; NTP, 1989).

Based on these studies, the major targets of pentachlorophenol toxicity seem to be the liver, kidneys and central nervous system. In the liver, pentachlorophenol produces pigmentation, increases liver weight and induces hepatic enzymes (Johnson et al., 1973; Schwetz et al., 1978; NTP, 1989). Effects on mitochondrial structure and cellular respiration have also been

reported (Fleischer et al., 1980; Gotz et al., 1980; NTP, 1989). The major renal effects of purified pentachlorophenol have been reported to be increased kidney weight (Johnson et al., 1973) and pigmentation (Schwetz et al., 1978). Reported effects on the central nervous system have included capillary congestion, chromatolysis of the nerve cells, diffuse focal areas of perivascular lymphocytes and mononuclear infiltration, and circumscribed subpial collections of unspecified small, round cells (McGavack et al., 1941).

Pentachlorophenol has not been shown to be carcinogenic in a number of studies (BRL, 1968a; IARC, 1979; Schwetz et al., 1978; Catillna et al., 1981); however, the studies are judged to be inadequate for assessment of human carcinogenic potential according to EPA's carcinogen risk assessment guidelines. Pentachlorophenol has been shown to be carcinogenic in studies in B6C3F1 mice using two different preparations of pentachlorophenol (NTP, 1989). Regardless of the level and nature of impurities present in the preparations, significant increases in the number of tumors in three major organ systems (i.e., digestive, vascular and endocrine) were observed. It has also produced negative results in an initiation/promotion study (Boutwell and Bosch, 1959).

A number of teratogenicity studies have failed to clearly establish a teratogenic potential for pentachlorophenol, though fetotoxic effects have been detected (Larsen et al., 1975; Hinkle, 1973). Female rat fetuses were more sensitive than males to the fetotoxic effects of a maternal dose of 30 mg/kg bw/day (Schwetz and Gehring, 1973; Schwetz et al., 1974b). The effects on the fetus may be a reflection of maternal toxicity, since the effects were observed at doses causing signs of maternal toxicity and the

placental barrier seems to be impermeable to pentachlorophenol (Larsen et al., 1975). The rat fetus appears to be more susceptible to pentachlorophenol fetotoxicity during early gestation in that Larsen et al. (1975) found the strongest fetal effect when pentachlorophenol was given on gestation day 9 or 10 and Schwetz et al. (1974b) found greater fetotoxicity when pentachlorophenol was given on days 8-11 compared to days 12-15 of gestation.

VI. HEALTH EFFECTS IN HUMANS

Clinical Case Studies

Nonfatal Exposures. Repeated exposure of the skin to sodium pentachlorophenate may produce dermatitis, systemic intoxication, and, in a limited number of people, an allergic response. Contact with the eyes can produce corneal damage, resulting in permanent impairment of vision (Dow Chemical Co., 1969a).

Acute toxicity has been reported in a number of studies following occupational exposure to pentachlorophenol. While these cases resulted from acute exposures, some of the symptoms may be related to chronic exposure at work.

Bergner et al. (1965) investigated four cases of nonfatal poisoning among factory workers at a Winnipeg plant. The major clinical symptoms observed were sweating, weight loss and gastrointestinal complaints.

Gordon (1956) reported four cases of nonfatal poisoning among herbicide sprayers in Australia. The onset of symptoms was characterized by abdominal pain, nausea and vomiting, with a profuse sweat developing shortly thereafter. In one case where the exposure occurred over a period of months, hepatic enlargement with possible reversible toxic myocarditis was observed.

Baader and Bauer (1951) investigated health complaints among workers involved in the production of pentachlorophenol in a West German plant. Reported complaints included severe skin eruptions, furunculosis, neuralgic pain and bronchitis. From these descriptions, it is possible that many of

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these symptoms resulted from dioxin contamination; however, the extent of contamination by chlorinated dibenzo-p-dioxins and dibenzofurans was not reported.

Other investigators have reported cases of acute poisoning following the home use of pentachlorophenol-containing products. These cases are less likely to involve chronic exposures than are the occupational exposures.

Chapman and Robson (1965) reported a case in which a 3-year-old girl was poisoned when an insecticide mixture contaminated the domestic water supply. Dermal contact was believed to be the major route of exposure. Symptoms included intermittent delirium, fever and convulsions. The clinical chemistry revealed acidosis, aminoaciduria and ketonuria. Her temperature returned to normal within 24 hours; however, aminoaciduria continued for 1 week.

Bevenue et al. (1967b) reported a case in which a male immersed his hands in a 0.4% pentachlorophenol solution for 10 minutes. The reported symptoms were localized redness and pain that persisted for 2 hours. Analysis of urine samples indicated that pentachlorophenol was absorbed through the intact skin and slowly excreted in the urine. After 3 weeks, urinary concentrations were still ~27% of the initial values.

Robson et al. (1969) and Armstrong et al. (1969) reported 20 cases of poisoning have also occurred following short-term exposure of neonates in a hospital nursery. These neonates evidenced signs of excessive sweating, tachycardia, tachypnea, respiratory distress, hepatic enlargement and

metabolic acidosis. In two of the infants who died, autopsy revealed fatty infiltration of the liver and fatty degeneration of the renal tubular cells. Exchange blood transfusion proved to be an effective treatment. Exposure was found to result from "percutaneous absorption of pentachlorophenol which had been used in the laundering of the diapers and the infants' bed linen."

Fatal Exposures. Three reports are available that describe the effects of fatal exposures in humans.

Bergner et al. (1965) described a case of pentachlorophenol intoxication in a 58-year-old male who had been employed for 1 week dipping wood into a petroleum solution, which reportedly contained 4.1% pentachlorophenol and 0.9% other unspecified chlorophenols. The individual initially experienced anorexia, fatigue, sweating, and thirst. The individual died after developing a temperature of over 106°F. An autopsy revealed slight centrilobular degeneration of the liver and mild renal tubular degeneration.

Gordon (1956) reported five fatal cases of pentachlorophenol poisoning among herbicide sprayers in Australia. Death generally occurred within 24 hours with a rapid change from a patient who is not remarkably sick to one who is completely moribund over the course of 1-2 hours. The observed symptoms were the same as in the nonfatal exposures.

Menon (1958) reported nine deaths over a period of 18 months among sawmill workers in Asia with known exposure to pentachlorophenol. Fever and profuse sweating were noted in all cases, but abdominal symptoms were much less severe than was reported by Gordon (1956). Severe terminal spasms occurred in all cases.

Epidemiological Studies

The effects of chronic occupational exposure to pentachlorophenol have been reported in a series of epidemiological studies in Hawaii (Klemmer, 1972; Takahashi et al., 1975; Begley et al., 1977; Klemmer et al., 1980).

Klemmer (1972) reported a study involving adult males occupationally exposed in wood-treating plants or as farmers/pest control operators to pentachlorophenol in Hawaii. The study included "over 300" volunteers, of which 152 were active at the time of the report. SGOT, SGPT and LDH levels were found to be elevated following chronic pentachlorophenol exposure. In a follow-up study, Klemmer et al. (1980) reported that lowgrade infections or inflammations of the skin and subcutaneous tissue, protective membrane of the eyes and the mucosal membranes of the upper respiratory tract occurred to a significantly greater extent in exposed groups as compared with control groups. The authors reported the following mean serum levels of pentachlorophenol in groups exposed in wood-treatment plants: 0.32 ppm in 32 controls, 1.92 ppm in 24 workers exposed to pentachlorophenol and other wood preservative chemicals, 3.78 ppm in 22 workers exposed to pentachlorophenol only. The authors concluded that no rangible effects occurred with blood chemistry and urine analyses from pentachlorophenol exposure.

A follow-up study by Gilbert et al. (1983) was comprised of a cohort comparison study and a historical analysis. The cohort portion of the study was designed to determine whether exposure to pentachlorophenol results in any clinically significant physiological effects. After a comprehensive health evaluation of wood treaters and their matched controls there were little differences in physical effects such as irritation to eyes, nose,

skin or upper respiratory tract, cardiovascular, gastrointestinal, genitourinary, neuromuscular, reproductive systems or mental disorders. There were no statistically significant differences in clinical or laboratory profiles between the control group and active wood treaters.

The long-term historical study concentrated on the incidence of cancer and death among workers exposed to pentachlorophenol between 1960 and 1981. The incidence of expected cancer in the wood treaters was no greater than the general population and there were fewer deaths than expected.

The U.S. EPA Position Document 4 evaluated this two part study (U.S. EPA, 1984). In the first portion the study consisted of primarily current workers and was therefore an inappropriate approach to assess a cancer risk, since it was likely that many of the workers who developed cancer while working had either died or left employment. The historical portion used a sample size that was too small and did not allow for a sufficient follow-up period in order to detect an excess risk of cancer. The Position Document 4 stated that because of limitations with the study no conclusion could be drawn regarding the potential cancer risks for wood [illegible] U.S. EPA 1984).

Takahashi et al. (1976) investigated the effect of pentachlorophenol on plasma protein levels in an unspecified number of workers in Hawaii. Using stepwise multiple regression analysis, chronic exposure to pentachlorophenol significantly ($p<0.05$) increased gamma mobility C-reactive proteins, which are often elevated in acute stages of inflammatory disorders or tissue

damage, total bilirubin, and creatine phosphokinase above the values observed in controls, although the latter two were considered to be within normal limits.

Begley et al. (1977) investigated the effect of pentachlorophenol on renal function among 18 workers at a Honolulu wood-treating plant. They found that creatinine clearance and phosphorus reabsorption were depressed, suggesting that pentachlorophenol reduces both glomerular filtration and tubular function. Both values demonstrated considerable improvement following a 20-day vacation, implying that these effects of pentachlorophenol on the kidney were reversible.

High-Risk Subpopulations

The available data are insufficient to clearly identify a high-risk human subpopulation. Available data from animal experiments indicate that the fetus and neonatal animal are particularly susceptible to pentachlorophenol toxicity, although the available data suggest that pentachlorophenol has a low teratogenic potential. The toxic response of newborns to acute exposures at what were probably low levels of pentachlorophenol indicates that the neonatal period may represent a time of heightened [illegible] for humans as well (Robson et al., 1969; Armstrong et al., 1969). However, current information, particularly on exposure, is inadequate for an assessment of the relative toxicity of pentachlorophenol between neonatal and adult humans.

Summary

Human exposure to pentachlorophenol results in local irritation, systemic effects, and, in a limited number of people, an allergic response (Dow

Chemical Co., 1969a). Pentachlorophenol poisoning is characterized by a profuse sweating, often accompanied by fever, weight loss and gastrointestinal complaints (Bergner et al., 1965; Chapman and Robson, 1965; Gordon, 1956). Liver and kidney involvement have been indicated in cases of fatal poisoning (Robson et al., 1969; Armstrong et al., 1969).

Epidemiological studies have revealed effects following occupational exposure to pentachlorophenol. One group of subjects also had a significantly increased incidence of low-grade infections or inflammations (Klemmer et al., 1980). Kidney function is depressed during chronic exposure, but these effects are at least partially reversible (Begley et al., 1977).

The available data are insufficient to identify a high-risk human subpopulation. However, animal data indicate that the neonatal animal and fetus are susceptible to pentachlorophenol toxicity.

VII. MECHANISMS OF TOXICITY

Uncoupling of Oxidative Phosphorylation

Gotz et al. (1980) determined the toxicity of pentachlorophenol in isolated rat hepatocytes, as measured by decreases in secretion of glutathione-sulfobromophthalein conjugates. The decreased secretion correlated with the uncoupling of mitochondrial respiration, implying that the hepatotoxic effects of pentachlorophenol may be due to an interference with the energy metabolism of the cell.

Weinbach and Garbus (1965) investigated the interaction of pentachlorophenol with rat liver mitochondria. They found that mitochondria could accumulate pentachlorophenol to concentrations greatly in excess of those necessary for the complete uncoupling of oxidative phosphorylation. Purified mitochondrial protein bound pentachlorophenol as well as the intact mitochondria, implying that "the protein-phenol interaction may be an important factor in the uncoupling phenomenon." Weinback and Garbus (1965) speculated that such interactions may induce configurational changes in the enzymes associated with oxidative phosphorylation or prevent the binding or rebinding of functional or structural factors necessary for this bioenergetic process.

In contrast, Leighty and Fentiman (1982) proposed that the effect of pentachlorophenol on oxidative phosphorylation results from binding to fatty acids in the mitochondrial membrane. They demonstrated the formation of a pentachlorophenol-palmitic acid conjugate in a coenzyme A fortified, rat liver microsomal system.

Interactive Effects

Pentachlorophenol pretreatment has been demonstrated to alter the toxicity of carcinogenic hydroxamic acids that are activated through the formation of sulfate esters (Meerman et al., 1980; Meerman and Mulder, 1981). N-hydroxy-2-acetylaminofluorene produces a periportal necrosis accompanied by increases in SGOT in male Wistar rats. A single i.p. dose of pentachlorophenol (40 μmol/kg bw), 45 minutes before administration of N-hydroxy-2-acetylaminofluorene, resulted in a complete inhibition of hepatotoxicity, presumably by the inhibition of N-O-sulfation (Meerman and Mulder, 1981).

Meerman et al. (1983) investigated the effect of repeated pentachlorophenol exposure on sulfation in male Wistar rats. The rats were fed diets containing 350 ppm (350 mg/kg diet, 17.5 mg/kg bw) sodium pentachlorophenate or given drinking water containing 1.4 mM sodium pentachlorophenate for 1 week. Both of these treatments resulted in a 30-45% decrease in the sulfation of harmol (compound that conjugates with inorganic sulfate or glucuronic acid that are excreted in bile and urine) and a 70-75% inhibition of the sulfation of the carcinogenic arylhydroxamic acid, N-hydroxy-2-acetylaminofluorene.

Pentachlorophenol appears to inhibit sulfation at the level of the cytosolic sulfotransferase, but the mechanism of this inhibition has not been elucidated (Mulder and Scholtens, 1977).

Pentachlorophenol also interacts with the carcinogenic amino-azo dyes in ways that apparently do not involve inhibition of sulfation. N-methyl-4-aminoazobenzene is believed to be activated through formation of a sulfate ester, resulting in the formation of three major DNA adducts (Tullis et al., 1981). Pretreatment with pentachlorophenol preferentially inhibits the formation of the N^6-deoxyadenosine adduct, although all three adducts are presumably formed through the sulfate ester intermediate (Tullis and Kadlubar, 1983). The mechanism of this interaction is unknown at this time.

Exon and Koller (1983a) have investigated the effect of several chlorinated compounds on ethylnitrosourea-induced transplacental carcinogenesis. Unlike 2-chlorophenol, no cocarcinogenic effect of pentachlorophenol was detected; however, the time to tumor (data not given) was decreased. This may be a result of the effects of pentachlorophenol on the immune system described in the Chronic and Subchronic Toxicity Section in Chapter V.

Pentachlorophenol has also been demonstrated to be an inducer of hepatic microsomal enzymes (Vizethum and Goerz, 1979). This effect would be expected to alter the toxicity of a wide variety of exogenous compounds, but this effect has not been specifically demonstrated.

Summary

Pentachlorophenol is an uncoupler of mitochondrial oxidative phosphorylation, resulting in an increase in the basic metabolic rate. This uncoupling presumably results from the interaction of pentachlorophenol with mitochondrial protein (Weinbach and Garbus, 1965), though Leighty and Fentiman (1982) proposed that conjugation with fatty acids in the mitochondrial membrane may be involved.

Pentachlorophenol has been demonstrated to reduce the toxicity of N-hydroxy-2-acetylaminofluorene by the inhibition of cytosolic sulfotransferase (Meerman et al., 1980; Meerman and Mulder, 1981) and is presumed to alter the toxicity of a variety of toxicants by the induction of microsomal enzymes (Vizethum and Goerz, 1979). In addition, pentachlorophenol appears to alter the binding of N-methyl-4-aminoazobenzene to hepatic DNA by a mechanism other than inhibition of sulfation (Tullis and Kadlubar, 1983).

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Introduction

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{[Uncertainty Factor(s) x Modifying Factor]}} = ____ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner,

the U.S. EPA (1986b) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty Factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effect and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{(\text{RfD}) \times (\text{Body weight in kg})}{\text{Drinking Water Volume in } \ell\text{/day}} = ____ \text{ mg/}\ell$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{(\text{NOAEL or LOAEL}) \times (\text{bw})}{(\text{UF}) \times (___\ \ell\text{/day})} = ____ \text{ mg/}\ell$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these

estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is

uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

1-Day Health Advisory. The data considered usable for the derivation of a 1-day HA are summarized in Table VIII-1. As can be seen from this table, these data are essentially confined to acute or short-term toxicity studies done with rats.

The study by Nishimura et al. (1982) provides a dose range indicating a dose producing no effect and doses producing effects, namely in the liver, after a single oral treatment. Sodium pentachlorophenate instead of pentachlorophenol, which was the test material used in other studies considered for HAs, was evaluated in this study. However, this study utilizes a dosing regimen closest to that expected with a 1-day exposure to humans, and the target organ effect is a toxicological endpoint applicable to both a 10 kg child and a 70 kg adult.

TABLE VIII-1

Effects of Acute Exposure to Purified Pentachlorophenol

Species	Route	Duration of Exposure	Dose (mg/kg bw/day)	Severity Level	Effects	Reference
Rat	oral	1 day	60	LOAEL	Reduced fetal weight when administered on day 9 or 10 of gestation.	Larsen et al., 1975
Rat	oral	1 day	10[a]	NOAEL	No effect on liver weight.	Nishimura et al., 1982
			30	NOAEL (LOEL)	Increased liver-to-body weight ratio	
			60	NOAEL	Highest dose that did not result in increased hepatic glycogen levels.	
			120	LOAEL	Lowest dose that produced a significant increase in hepatic glycogen levels.	
Rat	oral	10 days	5	NOAEL (LOEL)	Delayed ossification of the skull, but no skeletal or soft-tissue anomalies.	Schwetz and Gehring, 1973; Schwetz et al., 1974b
			15	LOAEL	Skeletal and soft-tissue anomalies in the fetus.	
			30	FEL	Fetotoxicity, altered sex ratio, skeletal and soft-tissue anomalies in the fetus.	
Rat	oral	7 days	17.5[b]	NOAEL	Inhibition of hepatic sulfotransferases.	Meerman et al., 1983
Rat	i.p.	15 days	30	FEL	Enlargement of the sinusoids, increased heterochromatin/euchromatin ratios, increased number of nucleoli/hepatocyte. Altered mitochondrial morphology.	Fleisher et al., 1980
Mouse	oral	1 day	5	NOEL	Altered intestinal absorption of D-glucose. This is a free-standing NOEL. No dose was reported at which pure pentachlorophenol altered intestinal absorption.	Madge, 1981

[a]Sodium pentachlorophenate was the test material. Doses were indicated as pentachlorophenol by the authors.

[b]Sodium pentachlorophenate was the test material

The liver effect at the lower doses in the Nishimura et al. (1982) study was confined to an increase in liver-to-body weight ratio, and this particular endpoint is identified as a NOAEL (LOEL) in that there could be a question of whether increased liver-to-body weight ratio by itself is an adverse toxicological effect (the authors suggested that it could be due to an increase in cell mass). However, the 10 mg/kg dose in the Nishimura et al. (1982) study did not induce any observable effect (NOAEL). The study by Larsen et al. (1975) suggests that the fetotoxicity of pentachlorophenol may not be as severe in rats when given for 1 day during organogenesis instead of during longer periods of organogenesis, but further investigation of this comparison is needed.

Although the effect levels are lower in the teratology study by Schwetz and Gehring (1973) and Schwetz et al. (1974b) than in the study by Nishimura et al. (1982), the 5 mg/kg and 15 mg/kg treatments in the teratology study were administered over the entire period of organogenesis (days 6-15), in contrast to the single dose administered by Nishimura et al. (1982). Although 30 mg/kg produced similar fetotoxicity whether given during gestation days 6-15 or 8-11 in these studies, lower doses were tested only during the longer period of gestation (days 6-15). The 10-day HA subsequently described would more closely approximate the repeated dosing pattern used in the teratology studies, and the no-effect level used in the 10-day HA calculation is below the lowest dose level used in the teratology studies. Furthermore, in contrast to the fetal skeletal effects noted in the teratology study by Schwetz and associates (where dams were dosed by gavage during organogenesis), the reproduction study by Schwetz et al. (1978), discussed below, produced skeletal anomalies in weanling rats necropsied on day 21 of

lactation, after treatment throughout gestation and lactation when dams were administered 30 mg/kg but not 3 mg/kg of pentachlorophenol in the diet. Schwetz et al. (1974b) concluded that a commercial grade of pentachlorophenol (88% pure) did not produce fetotoxicity at a dose level of 5.8 mg/kg with the same protocol used for testing purified pentachlorophenol (98%+ pure) in their teratology study. There may be a question as to whether the single effect of delayed skull ossification with 5 mg/kg of purified pentachlorophenol is a NOAEL (LOEL) or a LOAEL in view of the investigators' conclusion that this specific effect reflects a "mild nonspecific toxicity without definite consequence" (Schwetz et al., 1974a) and the Agency conclusion in Position Document 4 (U.S. EPA, 1984) that a NOEL was not established for either grade of pentachlorphenol in this study. However, considering that fetal effects were not evident with a lower dose level of commercial pentachlorophenol in the reproduction study by Schwetz et al. (1978), the 1-day and 10-day HAs are considered to be consistent with the toxicity data as discussed herein.

10-Day Health Advisory. Appropriate short-term studies are not available for the derivation of a 10-day HA for pentachlorophenol.

Longer-term Health Advisory. The studies considered in deriving the longer-term HA are summarized in Table VIII-2. The study by Schwetz et al. (1978) used a commercial purified grade of pentachlorophenol that contained the following components: chlorinated phenols, penta- (90.4%), tetra- (10.4%), tri- (<0.01%); dibenzo-p-dioxins, 2,3,7,8-tetrachloro- (<0.05 ppm), hexachloro- (1.0 ppm), heptachloro- (6.5 ppm), octachloro- (15.0 ppm); dibenzofurans, hexachloro- (3.4 ppm), heptachloro- (1.8

TABLE VIII-2

Effects of Short Term Oral Exposure to Purified Pentachlorophenol

Species	Duration of Exposure	Dose (mg/kg bw/day)	Severity Level	Effects	Reference
Rat	90 days	3	NOAEL	No increase in liver or kidney weight.	Johnson et al., 1973
		10	NOAEL	Increased liver weight, but no effect on kidney weight.	
		30	LOAEL	Increased liver and kidney weights. No pathologic changes at any dose level.	
Rat	~110 days	3	NOAEL	No statistically significant effects, but observations were consistently intermediate between control and 30 mg/kg bw/day groups.	Schwetz et al., 1978
		30	FEL	Reduced neonatal body weight, decreased percentage of live births, decreased survival of pups, decreased maternal body weight.	
Mouse	10-19 weeks	6.5	FEL	Enhanced development of splenic tumors following challenge with Maloney sarcoma virus transformed cells.	Kerkvliet et al., 1982a,b
Pig	30 days	5	NOEL	No effects on blood chemistry, organ weights or pathology of liver, kidney, spleen, brain and muscle.	Greichus et al., 1979
		10	NOAEL	Increased liver weight.	

ppm), octachloro- (<1.0 ppm); hexachlorobenzene (400 ppm). The data summarized in Table VIII-2 from the study by Johnson et al. (1973) are for a chemically pure pentachlorophenol, which contained no detectable level of any chlorinated dioxins. Greichus et al. (1979) used a purified pentachlorophenol for which their analysis of contaminants indicated 4.7% tetrachlorophenol, and 3.2 ppm total octachlorodibenzo-p-dioxins and furans. Independent analysis of this sample by Dow Chemical Company gave 0.98% tetrachlorophenol, and 0.4, 3.6 and 2.4 ppm of combined hexa-, hepta- and octachlorodibenzo-p-dioxins and dibenzofurans, respectively.

The results of these studies essentially show no or only minimal effects at doses ≤10 mg/kg/day. The practical significance of the observations by Kerkvliet et al. (1982a,b) of enhanced development of splenic tumors in mice may be questioned. The increased liver weight without pathological change at the 10 mg/kg dose in the Johnson et al. (1973) study is identified as a NOAEL (LOEL) in that there could be a question of whether increased liver weight by itself is an adverse toxicological effect. However, the studies by Johnson et al. (1973) and Schwetz et al. (1978) resulted in the same NOAEL (3 mg/kg/day) for different toxicological endpoints as well as effect levels at higher doses under the conditions of the studies. Johnson et al. (1973) obtained similar results with their "improved grade" of pentachlorophenol as described previously in Table V-2. Therefore, the studies by Johnson et al. (1973) and Schwetz et al. (1978) provide a consistent basis for calculating a 10-day HA. Additionally, the NAS (1977) used the 3 mg/kg NOAEL in the Johnson et al. (1973) study for a pentachlorophenol RfD calculation. The stuoy by Greichus et al. (1979) supports the effects on liver

weights found in rats by Johnson et al. (1973) by showing a slightly higher NOAEL of 5 mg/kg in pigs, given pentachlorophenol as a bolus in capsules.

Drinking Water Equivalent Level (DWEL). The studies considered in deriving the lifetime DWEL are summarized in Table VIII-3. The study by Catilina et al. (1981) involves s.c. dosing and is, therefore, of limited use in the derivation of a HA for drinking water.

The purity of the pentachlorophenol used in the study by Schwetz et al. (1978) has been described in the Longer-term Health Advisory Section. This is the best available study for the derivation of a lifetime DWEL in terms of the length of the exposure (22-24 months compared with 8 months for Goldstein et al., 1977) and the endpoints chosen (histologic examinations compared with hepatic enzyme levels).

Schwetz et al. (1978) maintained groups of 25 Sprague-Dawley rats of each sex on diets that resulted in a dose of 0, 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day for 22 (male) or 24 (female) months. At the termination of the study, observations included hematology, clinical chemistry, urinalysis, determination of organ weights, and gross and microscopic examination of tissues. At the high-dose level, increased SGPT activity and pigmentation of the liver and kidney were observed in both males and females. Decreased body weight and increased urine specific gravity were observed only in the females. At a dose of 10 mg/kg bw/day, pigmentation of the liver and kidneys was observed in the females, but not in the males. Schwetz et al. (1978) concluded that adverse effects were not observed in their 2-year chronic feeding study at dose levels of 10 mg/kg/day in male rats and 3 mg/kg/day in female rats.

TABLE VIII-3

Effects of Long-Term Exposure to Purified Pentachlorophenol

Route	Duration of Exposure	Dose (mg/kg bw/day)	Severity Level	Effects	Reference
Oral	8 months	5	NOAEL	No increase in glucuronyl transferase activity or decreased body weight.	Goldstein et al., 1977
		25	LOAEL	Increased glucuronyl transferase activity and decreased body weight.	
Oral	22-24 months	3	NOAEL	No histologic alterations of the liver or kidney.	Schwetz et al., 1978
		10	LOAEL	Pigment formation in liver and kidneys of females.	
		30	AEL	Pigment formation in the liver of males and females, and kidneys of females. Decreased body weight of females. Increased urine specific gravity in females. Increased SGPT activity in males and females.	
s.c.	40 weeks	6	NOAEL	Transient alteration in blood cell counts.	Catillna et al., 1981

Quantification of Noncarcinogenic Effects

Derivation of 1-Day HA. The study by Nishimura et al. (1982) with a NOAEL of 10 mg/kg/day based on liver effects is preferred for calculating a 1-day HA. Using the NOAEL of 10 mg/kg bw/day and an uncertainty factor (UF) of 100 for an animal NOAEL, a 1-day HA for a 10 kg child may be derived as follows:

$$\text{1-day HA} = \frac{(10\ \text{mg/kg/day})(10\ \text{kg})}{(100)(1\ \text{L/day})} = 1.0\ \text{mg/L}$$

where:

10 mg/kg/day	= NOAEL (Nishimura et al. 1982)
10 kg	= weight of protected individual (child)
1 L/day	= assumed volume of water consumed daily by a 10 kg child
100	= uncertainty factor appropriate for use with NOAEL derived from animal data and to protect sensitive members of the human subpopulation

This HA is equivalent to 1.0 mg/day or 0.10 mg/kg bw/day.

Derivation of 10-Day HA. There are no appropriate studies available for the derivation of a 10-day HA. If guidance is needed, it is recommended that the longer-term HA for a 10 kg child be adopted as the 10-day HA. The resulting HA would be 0.30 mg/L.

Derivation of Longer-term HA. The NOAEL of 3 mg/kg/day for renal and hepatic effects identified in the study by Johnson et al. (1973) and for reproductive effects found in the study by Schwetz et al. (1978) is preferred for calculating a longer-term HA. Using an uncertainty factor of 100 for an animal NOAEL, a longer-term HA may be derived.

For a 10 kg child:

$$\text{Longer-term HA} = \frac{(3\ \text{mg/kg/day})(10\ \text{kg})}{(100)(1\ \text{ℓ/day})} = 0.30\ \text{mg/ℓ}$$

where:

3 mg/kg/day	= NOAEL (Johnson et al. 1973; Schwetz et al. 1978)
10 kg	= weight of protected individual (child)
1 ℓ/day	= assumed volume of water consumed daily by a 10 kg child
100	= uncertainty factor appropriate for use with NOAEL derived from animal data and to protect sensitive members of the human subpopulation

For a 70 kg adult:

$$\text{Longer-term HA} = \frac{(3\ \text{mg/kg/day})(70\ \text{kg})}{(100)(2\ \text{ℓ/day})} = 1.1\ \text{mg/ℓ}$$

where:

3 mg/kg/day	= NOAEL (Johnson et al. 1973; Schwetz et al. 1978)
70 kg	= weight of protected individual (adult)
2 ℓ/day	= assumed volume of water consumed daily by a 70 kg adult
100	= uncertainty factor appropriate for use with NOAEL derived from animal data and to protect sensitive members of the human subpopulation

This HA is equivalent to 0.30 mg/day or 0.030 mg/kg bw/day.

These longer-term HAs are only slightly lower than the 1-day HAs. This is reasonable, since the pharmacokinetic data (Chapter III) indicate that pentachlorophenol does not appreciably accumulate during short-term dosing.

Assessment of Lifetime Exposure and Derivation of a DWEL. A DWEL may be calculated, based on the 24-month feeding study of Schwetz et al. (1978) that resulted in a NOAEL of 3 mg/kg bw/day. Using an uncertainty factor of 100 for an animal NOAEL, a DWEL may be calculated for a 70 kg adult.

Step 1 - RfD Derivation

$$RFD = \frac{3\ mg/kg/day}{(100)} = 0.03\ mg/kg/day$$

where:

3 mg/kg/day = NOAEL (Schwetz et al., 1978)

100 = uncertainty factor appropriate for use with NOAEL derived from animal data and to protect sensitive members of the human subpopulation

Step 2 - DWEL Derivation

$$DWEL = \frac{0.03\ mg/kg/day \times 70\ kg}{2\ \ell/day} = 1.1\ mg/\ell$$

where:

0.03 mg/kg/day = RfD

2 ℓ/day = assumed volume of water consumed daily by 70 kg adult

70 kg = weight of protected individual

The DWEL is equivalent to 2.1 mg/day or 0.030 mg/kg bw/day and is identical to the longer-term HA developed for a 70 kg adult.

Carcinogenic Effects

Data are currently available from two oral studies in which the carcinogenicity of pentachlorophenol has been assessed (BRL, 1968a; Schwetz et al., 1978). Pentachlorophenol was not found to be carcinogenic in either of these studies, even though doses that produced mild signs of toxicity were used. Catilina et al. (1981) also found no evidence of carcinogenicity in Wistar rats following s.c. administration; however, the dose level and length of exposure were limited in this study. Boutwell and Bosch (1959) also reported that pentachlorophenol is not a promotor of DMBA-induced skin carcinogenesis in Sutter mice. Recently, data became available from NTP

(1989) assessing the carcinogenicity of pentachlorophenol in mice. Significant increases in the incidence of similiar, biologically significant, tumor types were observed in mice fed two different grades of pentachlorophenol in the diet. Using the U.S. EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a), pentachlorophenol is classified as a group B2 chemical - probable human carcinogen - in light of "sufficient" evidence of carcinogenicity from animal studies along with "inadequate" evidence from epidemiologic studies.

Quantification of Carcinogenic Effects

Quantification of the carcinogenic potential of pentachlorophenol was performed using data from the recent NTP (1989) studies. An oral slope factor (q_1*) of 0.12/mg/kg/day was obtained by the pooled incidence of hepatocellular adenomas and carcinomas, pheochromocytomas, malignant pheochromocytomas, and hemangiosarcomas and hemangiomas in female B6C3F1 mice. The water concentration corresponding to a 10^{-4}, 10^{-5} and 10^{-6} lifetime risk is, assuming a drinking water intake of 2 ℓ/day, 30, 3 and 0.3 µg/ℓ, respectively. The U.S. EPA CRAVE Workgroup has reviewed and verified (verification date: 08/02/90) this carcinogenic potency estimate.

Existing Guidelines, Recommendations and Standards

Pentachlorophenol has been registered as a wood preservative since 1948. It is currently registered for agricultural use as a seed treatment for beans, alfalfa, clover, lespedeza and vetch, though the U.S. EPA (1984) has issued a notice of Rebuttable Presumption Against Registration (RPAR) for pesticide products containing pentachlorophenol (43 FR 48443-48477; 46 FR 13020). The ACGIH (1980, 1983) has established a threshold limit value

(TLV) of 0.5 mg/m³ and a short-term exposure level (STEL) of 1.5 mg/m³ for dermal exposure. U.S. EPA (1980) recommended an ambient water quality criterion of either 1.01 mg/ℓ based on the toxicity or 0.030 mg/ℓ based on the organoleptic properties of pentachlorophenol. The NAS (1977) calculated a safe drinking water level of 0.021 mg/ℓ using the 90-day toxicity study in rats by Johnson et al. (1973) and a 1000-fold uncertainty factor. The WHO (1984) has recommended a drinking water criterion of 10 µg PCP/ℓ.

Special Groups at Risk

Carcinogenic Contaminants. The Agency restrictions on pentachlorophenol as a wood preservative considered, with respect to health risks, the fetotoxic and reproductive effects of pentachlorophenol and the oncogenic risk from the HCDD and hexachlorobenzene contaminants. Although commercial pentachlorophenol contains residues of HCDD and other dioxins, the DWEL is based upon pentachlorophenol itself since the migration of the dioxins which are virtually insoluble in water would be considerably less than pentachlorophenol. Please note that TCDD has not been found to be a contaminant of pentachlorophenol.

Interactions. Pentachlorophenol may alter the toxicities of other compounds by three different mechanisms: immunological effects (see Chronic and Subchronic Toxicity Section in Chapter V), enzyme induction and inhibition of sulfation (see Interactive Effects Section in Chapter VII).

Vizethum and Goerz (1979) demonstrated the induction of microsomal enzymes by pentachlorophenol. While alteration of these enzymes by pentachlorophenol has not specifically been demonstrated to alter the toxicity of

other compounds, these types of alterations in enzyme activity, in general, may change the toxic potential of a wide variety of compounds.

Pentachlorophenol may also alter immune competence, thereby altering the effects of numerous challenges to the organism. The studies of Kerkvliet et al. (1982a,b) have indicated a possible enhancement of the development of splenic tumors in mice challenged with Maloney sarcoma virus transformed cells. No effect was observed on other indicators of immune function in this study.

The third way in which pentachlorophenol may alter the toxicities of other compounds involves the inhibition of cytosolic sulfotransferases (Mulder and Scholtens, 1977). Thus, compounds such as N-hydroxy-2-acetylaminofluorene, which are activated by the formation of a sulfate ester, are considerably less toxic in animals pretreated with pentachlorophenol (Meerman et al., 1980).

High-Risk Subpopulations. The data from human studies were insufficient to identify a high-risk subpopulation; however, limited data from animal studies indicate that neonates may be especially susceptible to the toxic effects of pentachlorophenol. Schwetz et al. (1978) cited an unpublished study by Dow Chemical Company in which the acute LD_{50} for 3- to 4-day-old rats (65 mg/kg) was less than half the LD_{50} for adult rats (~150 mg/kg). The reproductive studies of Schwetz et al. (1974b, 1978) have also consistently found greater effects in rat embryos than in the dams.

Summary

The 1-day, 10-day, longer-term HAs and DWEL are summarized in Table VIII-4. The HAs for a 70 kg adult are ≥1 mg/ℓ. However, Hoak (1957) has reported an odor threshold for pentachlorophenol of 857 ppb (0.857 mg/mℓ) at 30°C (86°F) and Dietz and Traud (1978) reported threshold levels of 30 µg/ℓ for taste and 1600 µg/ℓ for odor (20-22°C). It is possible, therefore, that water concentrations of pentachlorophenol that would result in levels of concern would also be unacceptable to the general population, based on organoleptic considerations. The lifetime adjusted acceptable daily intake may undergo revision when relative source contribution data are added to this document.

TABLE VIII-4

Health Advisories for Pentachlorophenol

Exposure	Health Advisory (mg/ℓ)	Reference
1-day (child)	1.0	Nishimura et al., 1982
10-day (child)	0.30	Johnson et al., 1973
Longer-term (child)	0.30	Johnson et al., 1973; Schwetz et al., 1978
Longer-term (adult)	1.1	Johnson et al., 1973; Schwetz et al., 1978
DWEL	1.1	Schwetz et al., 1978

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